Biopharmaceutical understanding of excipient variability in drug product performance

Zarmpi, Panagiota

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Biopharmaceutical understanding of excipient variability in drug product performance

Panagiota Zarmpi

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Declaration of any previous submission of the work

The material presented here for examination for the award of a higher degree by research has not been incorporated into a submission for another degree.

Candidate's signature

Declaration of authorship

I am the author of this thesis and the work described therein was carried out by myself, personally.

Candidate's signature

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(small and large cells) apparatuses. Bold values indicate significant differences between the test and the reference dissolution profiles ($f_2 < 50$).

List of Abbreviations

Abbreviation	Full Description
3D	3 dimensional
AAPS	American Association of Pharmaceutical Scientists
Abs	Absorbance
ACN	Acetonitrile
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
AU	Absorbance unit
AUC	Area Under the Curve
AUC_C	Control Area Under the Curve
AUC_R	Reference Area Under the Curve
AUC_T	Test Area Under the Curve
BCS	Biopharmaceutical Classification System
BET	Brunauer-Emmett-Teller
Ca^{2+}	Calcium
CBZ	Carbamazepine
CCS	Croscarmellose Sodium
CMA	Critical Material Attribute
CPP	Critical Process Parameter
CPV	Crospovidone
CQA	Critical Quality Attribute
CRS	Crystallinity

CV	Coefficient of Variation
$D_{crit(Y)}$	Maximum Tolerance Volume in the Y-plane
DmodY	Distance of observation to the model in the Y-plane
DoE	Design of Experiments
DP	Dicalcium Phosphate
DPA	Dicalcium Phosphate Anhydrous
DPD	Dicalcium Phosphate Dihydrate
DPL	Dipyridamole
$Drug_{aq.sol}$	Drug Aqueous Solubility
Exc.	Excipient
FaSSGF	Fasted State Simulated Gastric Fluid
FaSSIF-V2	Fasted State Simulated Intestinal Fluid (version 2)
FDA	Food and Drug Administration
FeSSGF	Fed State Simulated Gastric Fluid
FeSSIF	Fed State Simulated Intestinal Fluid
Fion	% of drug ionized
FRC	Functionality Related Characteristics
FRS	Furosemide
GC	Gas Chromatography
GF/D	Glass Microfiber Filter
GF/F	Glass Fiber Filter
GI	Gastrointestinal

HCl	Hydrochloric Acid
HCTZ	Hydrochlorothiazide
HPC	Hydroxypropyl Cellulose
HPLC	High-Performance Liquid Chromatography
HPMC	Hypromellose
IBU	Ibuprofen
ICH	International Conference on Harmonization
Inj. Vol	Injection Colume
IPEC	International Pharmaceutical Excipient Council
ITZ	Itraconazole
IVIVC	*In vitro-In vivo* Correlation
LED	Light Emitting Diodes
log P	log{octanol-water partition coefficient (P)}
LOWESS	Locally Weighed Scatterplot Smoothing
MCC	Microcrystalline Cellulose
MeOH	Methanol
Mg^{2+}	Magnesium
MgSt	Magnesium Stearate
Min	Minutes
MRI	Magnetic Resonance Imaging
MTF	Metformin
n	Number of replicates
NaCl	Sodium Chloride
NDA	New Drug Application

PEEK	Polyetheretherketone
PEG	Polyethylene Glycol
P-gp	P Glycoprotein
pKa	Logarithmic acid dissociation constant
PLS	Partial Least Squares
PRC	Paracetamol
PRESS	Minimum Predictive Residual Sum Of Squares
PSD	Particle Size Distribution
PTFE	Polytetrafluoroethylene
Q^2	Goodness of Prediction
QbD	Quality by Design
R^2	Goodness of Fit
RE	Relative Effect
Reauc	Relative Effect on AUC
REs	Relative Effect on drug solubility
RH	Relative Humidity
R_S	Reference solubility
R_t	Retention Time
R_T	Reference Cumulative Profile
S	Solubility
SA	Surface Area
SD	Standard Deviation
SDi	Surface Dissolution
SE	Standard Error

SEM	Scanning Electron Microscopy
SGF	Simulated Gastric Fluid
SLS	Sodium Lauryl Sulfate
SMX	Sulfamethoxazole
SSA	Specific Surface Area
SSG	Sodium Starch Glycolate
St	Standardized
Temp	Temperature
T_T	Test Cumulative Profile
USP	United States Pharmacopeia
UV	Ultraviolet
VIP	Variable Influence on Projection
Vis	Visible
Vs	Versus
WHO	World Health Organization
XRPD	X-ray Powder Diffraction

List of Units

% Percent

°C Celcium

°θ Angle

Å Angstrom

cN Centinewton

cP Centipoise

g Gram

h Hour

Kg Kilogram

kN Kilonewton

kv Kilovolt

M Molar

m2 Cubic meter

mA Milliampere

mg Milligram

Min Minute

mL Milliliter

mm Millimeter

mM Millimolar

mm2 Cubic millimeter

N Newton

nm nanometer

Pa Pascal

rpm Rotations per minute

s Seconds

Spm Strokes per minute

v/v volume per volume

w/v weight per volume

w/w weight per weight

µg microgram

µL Microliter

µm Micrometer

Abstract

Excipients present a challenge for oral drug bioavailability and it is recognized that excipient variability needs to be implemented in Quality by Design (QbD) approaches. The purpose of this thesis was to identify the biopharmaceutical implications of excipient variability on product performance. A systematic literature review identified the critical excipients (lubricants: magnesium stearate (MgSt), binders: hypromellose (HPMC), superdisintegrants: (sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CCS)) for oral drug performance and their critical material attributes that were further selected for experimentation. The impact of excipient variability on drug solubility and drug dissolution was examined using model compounds of different physicochemical properties. The effects of the varying composition of the gastrointestinal tract on the impact of excipients on product performance were examined by selecting compendial and biorelevant media and apparatuses of diverse hydrodynamics. Real – time surface dissolution UV imaging was used to characterize excipient behaviour under physiological conditions and to understand the mechanistic role of excipient variability on product performance. Excipient presence and variability affected drug solubility. MgSt and HPMC were considered excipients of high criticality for oral drug performance compared to superdisintegrants. Excipient effects on drug solubility strongly depended on drug physicochemical properties and medium characteristics. Cases where excipient variability may be critical for product performance were demonstrated with the design of roadmaps. Dissolution studies for a highly and a poorly soluble drug from tablets containing variant excipients revealed the criticality of MgSt variability (compared to HPMC and SSG) as faster drug dissolution for a highly soluble compound was observed when decreasing the particle size of MgSt. The influential role of pH, presence of solubilizing components and hydrodynamics on the impact of excipient variability on drug dissolution was revealed. Finally, the visualization of the surface events of superdisintegrant (SSG, CCS) swelling and their impact on drug dissolution revealed that the effects of superdisintegrants on drug dissolution strongly depend on excipient critical material attributes, drug aqueous solubility and pH of the medium. Throughout the studies of this thesis, the use of multivariate data analysis identified the critical biopharmaceutical factors of excipient variability with a potential risk for oral drug absorption.

Aims and Objectives

The aim of this project was to design biorelevant tests to understand the impact of key formulation excipients on drug solubility and dissolution performance and use these tests to generate a body of knowledge on the impact of varying excipient material attributes on product performance.

The key objectives included:

Chapter 1: Present the current knowledge on the issue of excipient variability. Identify the critical material attributes of key excipients currently used in immediate release formulations and their implications for oral drug performance.

Chapter 2 – 4: Investigate the effects and criticality of lubricant (chapter 2), binder (chapter 3) and superdisintegrant (chapter 4) variability on the apparent drug solubility in a biopharmaceutical perspective. Identify the biopharmaceutical implications of excipients on product performance by selecting model compounds of various physicochemical properties and media simulating the gastrointestinal conditions. Assess excipient criticality on oral drug performance with the use of multivariate data analysis and design of roadmaps.

Chapter 5: Delineate the impact of excipient variability on *in vitro* drug dissolution by producing immediate release tablets with excipient variants using a highly and a poorly soluble model compound. Identify the role of excipients on drug dissolution in a biorelevant perspective by selecting diverse media (compendial/biorelevant) and hydrodynamic conditions (compendial apparatuses and surface dissolution UV imaging). Assess excipient criticality for drug dissolution using multivariate data analysis.

Chapter 6: Assess the effects of critical material attributes of superdisintegrants on the excipient swelling performance and on drug dissolution. The impact of superdisintegrant variability on excipient performance and drug dissolution in acidic and basic media was investigated with the use of real – time surface dissolution UV imaging.

Title: Biopharmaceutical aspects and implications of excipient variability in drug product performance

Author: P. Zarmpi,T. Flanagan,E. Meehan,J. Mann,N. Fotaki

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Chapter 1 Preface

Based on the pharmaceutical Quality by Design (QbD), the scientific understanding and risk assessment of the components and processes affecting final product specifications is a prerequisite for achieving final product quality. Critical material properties or process parameters are identified and controlled to assure the delivery of safe and efficient final dosage forms. Excipients are substances, commonly used in solid oral dosage forms, as they enhance drug product processing during manufacturing and/or assist the effectiveness and delivery of the drug into the systemic circulation. Variation in material properties of excipients can impact drug dissolution and thereby in vivo performance and it is widely recognised that the impact of excipient variability should be considered as part of a QbD approach to product development. The mechanisms by which excipients affect product performance and how this may be influenced by changes in excipient material properties is poorly understood during formulation selection for both immediate or extended release formulations. It is, therefore, beneficial to gain a detailed understanding of the impact of the molecular, structural, particle properties and level of excipients on product performance. The biopharmaceutical implications of excipient presence and variability need also to be considered in the QbD concept, as excipient performance may alter or be altered by the heterogeneity of the gastrointestinal lumen. Towards this goal, a literature review (Chapter 1) is presented summarizing the current knowledge of the issue of excipient variability on product performance. Commonly used excipients in immediate release formulation (diluents, binders, lubricants, superdisintegrants) are discussed in order to understand their critical material properties and potential biopharmaceutical implications that could influence product performance.

Chapter 1. Biopharmaceutical aspects and implications of excipient variability in drug product performance (Literature Review)

Abstract

Implementation of Quality by Design approaches in pharmaceutical industry requires a sound understanding of the parameters triggering final product variability. Excipients, although generally regarded as inert components, are of great significance in terms of solid dosage form development and any variation in the material attributes may impact drug product performance. Sourcing, production and processing are contributing factors to excipient variability. Interchange between different suppliers can lead to final products with different quality attributes. Identification of excipient critical material attributes is not straightforward, as criticality must be linked to functionality and it is well recognized that the mechanisms by which excipients exert their action are not fully understood. Investigating the impact of excipient variability on *in vitro* dissolution could enable scientists to get an insight on the *in vivo* behaviour of drug products and potentially tolerate variability. A thorough understanding of excipient material properties, product components interactions and the effect of the gastrointestinal tract heterogeneity on excipients and drug release is recommended. This review aims to present current knowledge on excipient critical material attributes and their link to biopharmaceutical behaviour and dissolution characteristics. Attempts to describe the impact of physiological conditions on excipient functionality are also addressed. Excipient properties that are considered crucial to drug product performance in a biorelevant perspective are elucidated.

Keywords: Excipients; Dissolution; Solid Dosage Form; Solubility; Gastrointestinal; Polymers; Variability.

1.1.Introduction

Pharmaceutical development is now entering the new era of quality build. The traditional three batch validation is currently fading as batch failures, product recalls, drug shortages are still present in the pharmaceutical market. Regulatory agencies tend to impose more strict product specifications for new drug applications (NDAs), abbreviated new drug applications (ANDAs), biowaiver extensions and require a profound understanding of active pharmaceutical ingredient (API), excipient and product manufacturing, as well as, any interaction between these parameters that may affect final product safety and efficacy. In an attempt of amelioration, pharmaceutical industry is implementing the principles of Quality by Design (QbD). The aim is to build robust manufacturing processes in order to assure that the desirable product is constantly delivered to the patient through the establishment of a design space that defines the permissible area where variability and/or variations of input materials will not affect the outcome of the production process. Reducing or tolerating final product variation requires a profound understanding of all factors playing a crucial role in finished dosage forms. Controlling these crucial parameters will allow the design of products that will consistently meet final requirements, contribute to minimization of regulatory constraints and enable the safe passage from batch to continuous manufacturing, a beneficial production technique to address industrial deficiencies [1]. Excipients constitute a major component of final products and it is recognized that variability in their material properties can impact product processing, manufacturing and performance [2, 3]. The exact mechanisms by which excipients exert their action are still to be discovered, especially when drug product performance is concerned [4, 5]. The gastrointestinal heterogeneity and its effect on excipient functionality is an additional challenge in understanding and controlling the role of excipients in drug release.

A comprehensive overview of the current knowledge on excipient variability and its effect on solid dosage form performance is presented in this review. The biopharmaceutical parameters that impact the functional role of key excipients used in solid formulations is discussed. The aim is to gain a basic understanding of potential critical material attributes and their link to excipient and final drug product variability.

1.2. Excipient variability in drug development

As mentioned in the International Conference on Harmonization (ICH) Q8 "the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product" [6]. A final dosage form should meet a number of specifications to justify its efficacy and safe use. Deviation from these acceptance criteria indicates variability of final dosage forms. Variation is difficult to control since random distribution prevails in everything [7]. QbD aims towards controlling variability by i. defining the final product attributes that will justify the intended use of final products and ii. deliberately designing the production process and establishing the design space and control strategy to always meet these final attributes. Aspects whose variability can compromise product quality are characterized by high criticality. Critical quality attributes refer to aspects of the output product while critical material attributes to input materials [8]. In terms of pharmaceutical development, factors that may trigger final product variability include: active pharmaceutical ingredients (APIs), excipients and process parameters [8]. The physicochemical properties of the two former, any deviations or alterations in the latter and the complex interplay of process parameters and material attributes contribute to the incline in quality specifications. It becomes clear that in order to control the outcome we must have a fundamental understanding and control of all input materials. The required understanding of the reasons triggering product variability and batch failures is needed towards continuous pharmaceutical production and may not always be an easy task [9].

The impact of manufacturing processes on drug product quality has been addressed [10-12] but a more comprehensive approach towards drug product components is yet to be made. Examining the effect of input materials (e.g. APIs and excipients) on finished solid dosage forms requires a linkage of material properties to product quality attributes [13]. A thorough understanding of molecular, structural and particle properties of a substance is necessary. The limited knowledge on the role of physical and chemical properties of pharmaceutical components hinders the possibility to further optimize the behavior of oral solid dosage forms throughout manufacturing, but this gap is more pronounced in drug product performance. A change in a critical attribute for dissolution will not only cause production or regulatory failures, but it may strongly affect drug bioavailability. The complexity of

the gastrointestinal environment adds a further challenge in investigating the effect of material attributes variability in drug dissolution. Although the API is considered the most substantial product component for disease treatment, it has to be noted that excipients can be more important in processes prior to oral drug absorption and also can induce even treatment failure if the drug is not appropriately released and dissolved according to product specifications. From manufacturing through to in vivo functional performance, excipients exert their action but their properties can affect drug dissolution, as it will be revealed by the critical analysis performed in this review. Since excipients constitute a large portion of a solid dosage form, comprising up to 99% of the total formulation mass [14], their impact on quality attributes can be statistically significant. The broad range of the excipient level used in solid dosage forms along with a possible alteration in excipient functionality by level variation, complicates further the excipient variability issue. *In vitro* and/ or *in vivo* excipient effects on drug solubility, dissolution and permeability could impact oral bioavailability and bioequivalence. The use of a different type of excipient with the same intended functionality could also be problematic as the diversity of material properties may result in a change of the overall product performance. Understanding and integrating excipient variability in the production's design space and control strategy will pave the way for building robust production processes both in batch and continuous manufacturing [15].

1.3. Sources of excipient variability

Final product variability either preexists or is created during manufacturing. In this review, we are focusing on inherent excipient variability and its effect on final drug product. The main reasons for excipient variability are: i. raw material sourcing which includes environmental variations that may lead to different raw material properties and ii. manufacturing which refers to excipient variability caused by a change during excipient production and can be divided into inter and intra-supplier.

Natural sourcing: The majority of excipients are naturally derived products or semi-synthetic compounds (produced after chemical modification of a natural product). They are bound, therefore, with inevitable variability caused by environmental alterations (natural, regional, seasonal) [16]. Sourcing of raw materials is a major factor for excipient variability. For example, microcrystalline cellulose can be produced by wood (softwood/hardwood) or cotton. A first study on four brands of

microcrystalline cellulose (two brands derived from softwood and two from hardwood) examining lignin and hemicellulose content determined excipient origins. Significant variations in chemical structure, crystal structure and particle size were observed [17]. Differences in lignin content may be the cause for the increased dissolution rate of prednisone tablets manufactured with microcrystalline cellulose from different sources [18]. Controlling the source of excipients can reduce variation but still any unavoidable natural complications may lead to production of different raw materials.

Manufacturing: Excipients are manufactured by chemical companies for use in pharmaceutical, chemical, and food industry. A common strategy for pharmaceutical companies is to have more than one supplier in order to constantly meet market demands [14]. Changes in excipient supplier has been shown to contribute to excipient variability. Supplier to supplier variability may arise either from different natural sourcing or different manufacturing processes. For instance, significant intersupplier variability was observed in anhydrous lactose solid state properties (specific surface area, tensile strength, yield pressure) that could impact final dosage forms according to the amount of excipient used and the interplay with the other dosage form components [19]. Other examples of intersupplier variability are reporting differences in intrinsic viscosity, mean molecular weight, mean particle size and water uptake rate between two interchangeable Hydroxypropyl cellulose (HPC) brands [20], and in particle size and surface area between different magnesium stearate suppliers [21]. Although, intersupplier variability may seem more reasonable, intrasupplier variability referring to batch-to-batch or lot-to-lot variation in excipient production has been reported as well. A notable example of interlot excipient variability and its effect on final dosage form refers to a study by Perez et al. on lot to lot variability of Carbomer 943. The two dissimilar lots were found to greatly affect *in vitro* release rates of hydrochlorothiazide (HCTZ) matrix tablets, due to differences in mean molecular weight of carbomer [22]. Even a slight change in manufacturing procedures or parameters may have an effect on the product functionality. For example, two batches of soluble starch differing only in one additional washing step with acetone were studied. Although, in terms of routine characterization the two batches were found identical, their compaction properties showed large variation due to their differences in the surface area caused by the extra washing step [23].

Inadequate specifications: Pharmacopeial specifications clearly address excipient identification but functionality specifications are not straightforward since excipient function is formulation/application dependent [3]. For instance, when hypromellose is used as a binder, viscosity and degree of substitution are considered functional properties, but additional properties (particle size distribution, powder flow) need to be controlled when the excipient is used as a release modifier [24]. Excipient demand is increased in the Food/Chemical/Cosmetic Industry, and the quality tests prescribed to suppliers assuring excipient quality (identity, quality, purity) [3] focus mainly on their needs. This minimum of regulatory specifications may suffice for these industries, but pharmaceutical companies have to deal more strictly with excipient variability and be assured that the properties rendering excipients functional are "present" in every batch within appropriate limits. A first issue that arises from current monograph specifications is that they cannot adequately set the appropriate limits in functional specifications ("one-point" limits [25] or a wide range of acceptance values). Without prior mechanistic knowledge of the actual excipient role, variability could be detrimental, even if excipient property values meet monograph specifications [25]. The need for functional evaluation is encouraged with the introduction of Excipient Functionality Related Characteristics (FRCs) by the European Pharmacopeia and the General Information Chapter on "Excipient Performance <1059>" by the United States Pharmacopeia. Still, the terminology of excipient functionality is not straight-forward. The underlying mechanisms of excipient use in several cases are not known and further investigations are necessary in order to establish functionality tests, as excipient role should be addressed in case-by-case, function-by-function and product component interactive perspective. The proposed FRC tests are not mandatory and mostly address chemical identification rather linking physical and chemical properties to excipient function [3]. Drug product manufacturers should gain a more thorough knowledge on excipient production and characteristics to get an insight when changing excipient suppliers in order to assure that excipient functionality and material properties remain consistent.

1.4. Biopharmaceutical aspects of excipients

Formulation scientists recognize the importance of excipient variability in drug product design. Reports in literature though address mainly drug product processing/manufacturability [26] and not drug product performance in terms of drug

release from a solid dosage form and drug bioavailability. An interplay between *in vitro* conditions (i.e. dissolution medium composition, temperature, agitation) and in vivo physiological factors (i.e. gastrointestinal factors) and excipient functionality can impact drug bioavailability (**Figure 1.1**). Excipient presence in the luminal fluids triggers modifications in the gastrointestinal environment and gastrointestinal conditions may alter excipient material attributes leading to different functionality, with an effect in drug absorption in both cases. This strong interplay will complicate even more final product variability and bioequivalence, if not thorough investigated.

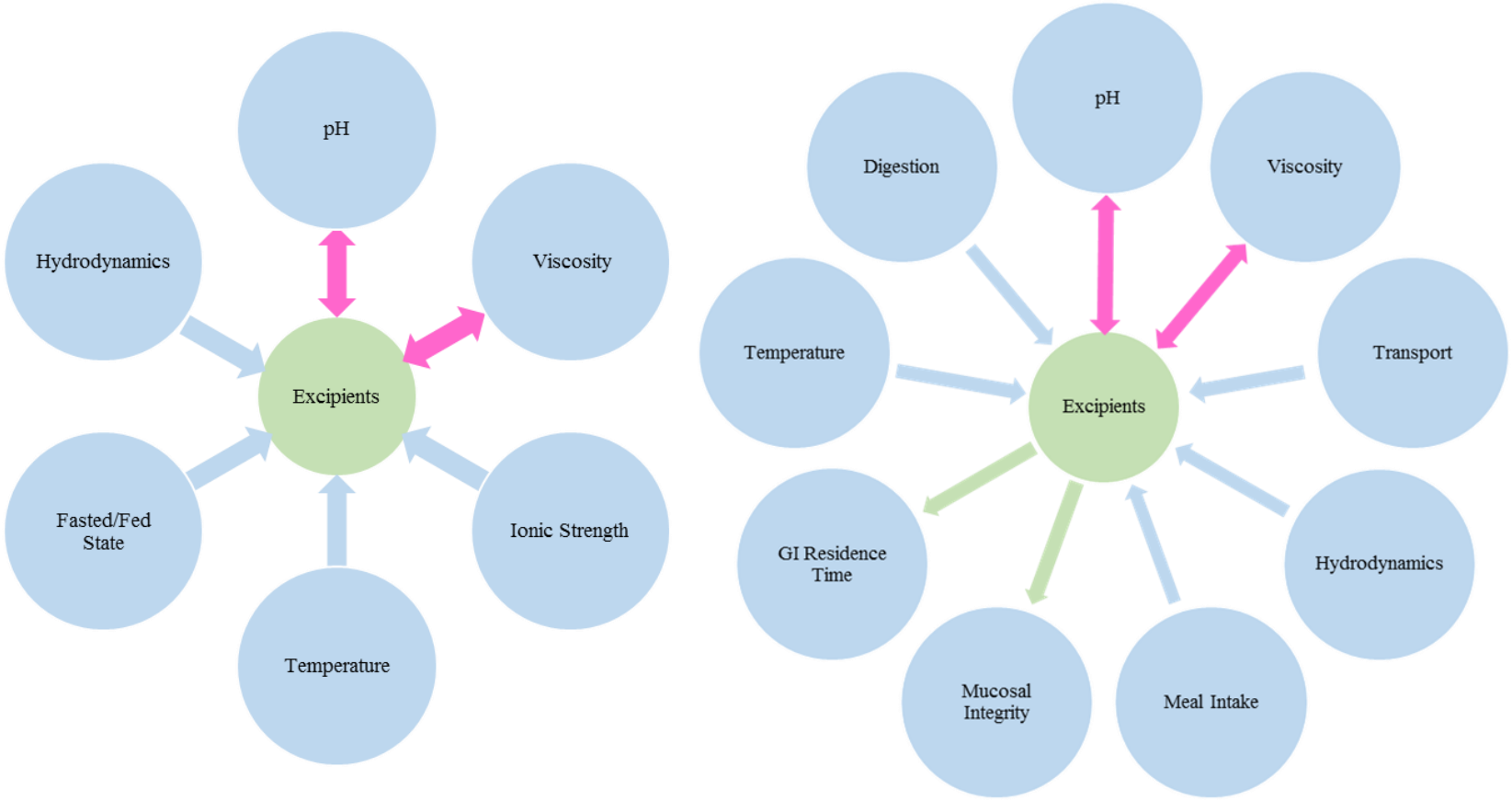

Figure 1.1: A. In vitro (dissolution test) and B. in vivo (gastrointestinal environment) factors reported to affect or be affected by the presence of excipient in the gastrointestinal lumen.

1.4.1 Effect of excipients on physiological conditions

Traditionally the effect of excipients, on drug product performance was considered of minor importance, due to their pharmacological inactivity. Only after the beginning of 90s, and with the foundation of the International Pharmaceutical Excipient Council (IPEC), investigation of their significance on finished drug products started [27]. An increased number of case studies indicate that excipients may influence bioavailability and impede the establishment of bioequivalence between products. Novel formulations addressing the poor aqueous solubility of drugs, contain excipients that affect drug solubility, permeability (passive or active) and metabolism [28]. Solubilizers enhance the solubility of poorly soluble drugs and may decrease drug permeation through the intestinal epithelium due to the lower free drug fraction available for absorption [29]. A number of excipient classes have been demonstrated to affect tight junction integrity [30], active transporters, [31, 32] and cytochrome P450 activity [33, 34]. Excipient effects on other physiological factors, e.g. gastric residence time, small intestinal transit time, mucus integrity, physiological pH and motility, have been extensively reviewed [35]. These interactions present a challenge on current considerations about the role of excipients on product performance and regulatory guidelines require extensive proofs of excipient inertness in each product [36, 37]. Biowaivers have been correlated to the Biopharmaceutical Classification System (BCS), and qualitatively and quantitatively similar excipients are required for biowaivers for immediate release formulations of BCS Class III compounds [37, 38]. According to WHO guidelines, an excipient can be used in multisource (generic) products requesting biowaiver even if it is not present in the comparator product, as long as it is present to other products containing the same API and have marketing authorization in countries participating in the International Committee of Harmonization [39]. Even in cases where excipients were not implied to affect bioequivalence, human bioavailability was altered with a change in the amount of an excipient or the addition of a new excipient in the generic product [40]. The addition of Sodium Lauryl Sulfate in a generic alendronate immediate release tablet (absent in the innovator alendronate (BCS III) tablet but present in generic alendronate tablets approved in USA) led to a 5-6 fold increase of alendronate's bioavailability resulting in bioinequivalence [40]. Drug permeability can be affected or not by the presence of excipients as revealed by *in vitro* permeability studies (Caco-2 models). The presence

of lactose, HPMC and PEG did not alter the permeability of BCS Class III compounds [41]. A drug dependent excipient effect has been shown in the case of Tween 80 due to its P- glycoprotein (P-gp) inhibitory effect, as it increases the apparent permeability (Papp) of drugs that are P-gp substrates (e.g. cimetidine) while other drugs remain unaffected (e.g. atenolol, acyclovir) [42]. Sodium Lauryl Sulfate (SLS) shows a concentration-dependent effect on the permeation of low permeability drugs with an increase in the Papp when present in low concentrations (0.139 mM) [42] while at increased concentrations drug permeation is even greater due to excipient-mediated disruption of the cell monolayer [41, 42]. The in vivo impact of excipients on drug permeability has to be further investigated, as *in vitro* permeation models (such as Caco-2 monolayers) are more sensitive in excipient effects and may overestimate their impact [41]. Generalized conclusions should be avoided without prior scientific knowledge on the biopharmaceutical aspects of excipients. Although, there is a tendency to investigate the effect of excipients with a prominent role on dissolution and bioavailability (surfactants, carriers, bioadhesives, polymers, copolymers etc.), the intended product performance can be compromised even from excipients whose initial role is not related to drug release/dissolution [40].

1.4.2 Effect of physiological conditions on excipients

When formulating a solid dosage form, the varying composition and heterogeneity of the gastrointestinal tract need to be considered. Factors such as properties of the gastrointestinal contents (i.e. pH, ionic strength, temperature, viscosity, bile salts concentration) and gastrointestinal motility will have an impact on drug release. Gastric emptying will influence drug, excipient and product characteristics. Moving from the acidic stomach to the more basic small intestine affects the ionization and solubility of weak acidic/basic drugs and subsequently their absorption. Moreover, the changes in physiological conditions by the presence of meal (fed state) can alter solid dosage form performance. Excipient properties and their functionality will be impacted by this heterogeneous environment (data indicating the effect of physiological conditions on excipient functionality is discussed in detail in the next sections of this review). Excipient variability should be addressed in a biorelevant perspective reflected in *in vitro* dissolution testing. The use of biorelevant media mimicking physiological gastrointestinal aspects in fasted and fed state (i.e. bile secretion, meal components, surface tension, osmolality) [43, 44] could enable the

investigation of the gastrointestinal effect on excipient functionality and drug release. A better understanding of the complex excipient effects taking place in the gastrointestinal tract and their impact in product performance could be achieved by the combination of biorelevant *in vitro* dissolution testing with imaging techniques, where applicable [45].

1.5. Excipients in solid dosage forms

Particle size distribution, pore size distribution and surface area are critical properties for dissolution of solid dosage forms [13], but not the sole ones. In the following sections material properties of commonly used excipients in solid dosage forms are discussed, revealing their functional role on drug product performance. Excipients are categorized according to their function in solid dosage forms (**Table 1.1**) and cases related to their functionality or variability are reviewed.

Table 1.1: Material properties related to excipient variability

		Diluents		**Binders**		**Lubricants**	**Disintegrants**		
		Lactose	DP	MCC	HPMC	Magnesium Stearate	SSG	CCS	Crospovidone
Molecular Properties	Composition				✓	✓	✓	✓	
	Hydration	✓	✓			✓			
Structural Properties	Polymorphism	✓	✓	✓		✓			
Particle Properties	Particle size	✓		✓	✓	✓	✓	✓	✓
	Surface area	✓		✓		✓	✓	✓	✓
	Size distribution	✓			✓		✓	✓	✓
Level		✓	✓	✓	✓	✓	✓	✓	✓

DP: Dicalcium Phosphate, MCC: Microcrystalline Cellulose, HPMC: Hydroxypropyl Methylcellulose (Hypromellose), SSG: Sodium Starch Glycolate, CCS: Croscarmellose Sodium

1.5.1 Diluents

Diluents, referred also as fillers, are incorporated into solid dosage forms to adjust their mass. When low drug doses are required, fillers may comprise up to 90% of the total dosage weight to ensure adequate product processability throughout manufacturing. Despite the simplicity of their role, their high concentrations may render them high risk factors for product performance. Their physical and chemical properties are significant attributes for their functionality and may trigger dosage variability, but their impact is usually related to other product components. Diluents can be either inorganic or organic materials. Typically used diluents include: lactose, mannitol, microcrystalline cellulose and dicalcium phosphate [46].

1.5.1.1 Lactose

Lactose is a disaccharide consisted of D-galactose and D-glucose units linked through a β (1-4) glycosidic bond and is produced from bovine milk. Lactose is mainly used as soluble diluent in formulations, but it possesses binding properties as well [47].

Molecular Properties

Two anomeric forms of lactose, referred as α and β, are present, according to glucose stereochemistry. An interchange between the two isomers, called mutarotation, is observed in aqueous solution. When in equilibrium (0-100 °C), the ratio between the two forms is approximately 60:40 for β and α lactose, respectively. They differ in physical properties such as melting point, density, specific optical rotation, and on solubility with β lactose being more soluble in water (20 °C; 0.5 g/mL) than the α anomer (0.075 g/mL) [48]. The α isomer, according to temperature, may exist as monohydrate (<120 °C) or anhydrous (>120 °C) form, while β lactose is anhydrous [48]. These molecular differences affect lactose's solid state properties and products with varying attributes are available on the market. Presence of impurities in lactose brands may catalyze drug hydrolysis, affecting drug stability [49].

Structural Properties

Varying crystallization patterns are observed due to the presence of the two anomers and their solubility difference. The α isomer crystallizes as a monohydrate in low temperatures (<93 °C) in a variety of shapes (prism, pyramidal, tomahawk) [47]. Uneven-diamond shape crystals of 80% β-lactose anhydrous with a small portion of

α-lactose anhydrous are formed with increased temperature (>93 °C) [48]. Spray-dried lactose, consisted of α-lactose monohydrate and amorphous lactose, in a spherical shape with excellent flow properties has also been produced. The structural differences lead to products with varying compactions forces [19]. Higher initial solubility and dissolution rate for the β-form was observed from different crystalline lactose powders in water at 37 °C, followed by a decrease in the order β-lactose (0.5 g/mL water) >α-lactose anhydrous (0.27 g/mL water) >α-lactose monohydrate (0.13 g/mL water) but due to mutarotation, final solubility for all lactose types was the same [47, 50]. Monohydrate α and β lactose disintegrated faster compared to anhydrous lactose and an increase in compression force resulted in increased disintegration time. The fast disintegration was attributed to the increased porosity of lactose tablets which allowed quick water penetration [50].

Particle Properties

Particle size distribution of lactose is not specified in pharmacopeias. Lactose brands with varying size distribution are available in the market [47]. When the effect of lactose particle size in product manufacturing was studied, it was shown that in direct compression, an increase in lactose particle size will enhance blend flowability and form weaker tablets [51], due to decreased cohesiveness of particles. Studies on wet granulation behaviour of lactose linked particle size and size distribution to granule porosity. Small particle sizes (53 μm) give granules with higher porosity, as a result of the higher resistance of small particles to densification [52]. Narrow ranges of particle size (40-75 μm, 212-250 μm) produced granules of higher porosity due to the absence of fine particles that tend to occupy void volumes between larger particles [52]. As porosity is considered an important parameter for water penetration, particle properties of lactose can have a major impact on dissolution.

Level

Lactose may greatly enhance dissolution of poorly soluble drugs as the soluble diluent improves powder and tablet wettability. Studies on ethinamate capsules showed a decrease in drug release when 10% w/w lactose was used in the formulation but improved dissolution when diluent concentrations reached levels of 50% w/w [53]. Increasing the percentage of fine lactose in indomethacin formulations (interactive mixture of API and coarse lactose) resulted in improvement of the drug's dissolution

rate, as rapid dissolution of lactose leaving open structures enables deagglomeration of indomethacin particles [54]. For a soluble drug (chloramphenicol) inclusion of lactose at 50% w/w in the capsule formulation had no effect on drug's dissolution. Increasing lactose to a level of 80% w/w slowed down chloramphenicol dissolution, as the dissolved diluent retards drug release [55]. The interplay between lactose content and drug's BCS class was recently portrayed in a top-down approach comparing marketed innovator and generic products with proved bioequivalence. For BCS class I and class III drugs relatively large differences in lactose level were observed whereas for BCS class II and class IV drugs small variations in these levels were noted. The probability of bioinequivalence based on these differences in lactose levels between the innovator and generic products was classified as low or BCS class I drugs, medium for BCS class II and III drugs and high for BCS class IV drugs [56].

Biopharmaceutical Properties

Lactose can affect bioavailability through a dissolution modification effect. No impact on other physiological factors has been reported [56]. Interactions between milk proteins and lactose have been described. Low lactose concentrations decreased the viscosity of the milk dispersion (lactose assembles around protein molecules) whereas high lactose concentrations increased the viscosity of the dispersion (reduction in water-protein interactions) [57]. The potential interplay of meal intake and lactose on physiological factors and drug release and dissolution has not yet been investigated in a biopharmaceutical perspective.

1.5.1.2 Dicalcium Phosphate

Calcium phosphate dibasic, or dicalcium phosphate (DP), is an inorganic insoluble diluent used in tablet and capsule manufacturing.

Molecular and Structural Properties

Two hydration forms of dicalcium phosphate, anhydrous (DPA) and dihydrate (DPD), are used in pharmaceutical development [58, 59]. The anhydrous form occurs as a triclinic crystal while the dihydrate forms a monoclinic structure [58, 59]. Dicalcium phosphate dihydrate presents good flow properties and low hygroscopicity. According to temperature (40-50 °C) and humidity (32-75% relative humidity) [60], though, it tends to lose water of hydration that may cause chemical instability of APIs

in dosage forms [61]. The anhydrous form presents an alternative without compromising drug stability. The two forms differ in porosity, as a result of their different hydration. The anhydrous form exhibits higher porosity due to the absence of water in the crystal structure, leading to its better compressibility and faster disintegration [62].

Level

As for lactose, the effect of dicalcium phosphate on drug release is profound in high levels of the diluent. Replacing lactose with dicalcium phosphate dihydrate or anhydrous resulted in decreased and extended release of alprazolam from matrix tablets containing HPMC as well. In binary systems containing different ratios of lactose and dicalcium phosphate dihydrate, increasing the amount of the insoluble diluent did not impact dissolution rate, and only when, dicalcium phosphate dihydrate was the sole diluent and in high level (36.5% w/w) drug dissolution was affected [63].

Biopharmaceutical Properties

The pH difference of the stomach and intestinal contents is expected to affect dicalcium phosphate's behaviour [64], due to its higher solubility in acidic media. In a comparative study on the effect of pH on superdisintegrant functionality (discussed in sections 1.5.4.1, 1.5.4.2, 1.5.4.3), the influence of different types of diluents on drug dissolution was evaluated. Swelling capacity of some disintegrants is lower in acidic medium, leading to reduced disintegration and dissolution. When lactose was the diluent, the reduced swelling of superdisintegrants caused a decrease in the dissolution of hydrochlorothiazide (HCTZ) tablets in acidic medium (0.1 N HCl, pH=1; paddle method, 50 rpm, 37 °C). Substituting lactose to DPD led to higher drug release in the acidic solution, compared to water and the effect of superdisintegrant swelling to reduce dissolution in acidic media was not observed (**Figure 1.2**) [65]. Although the overall dissolution rate of HCTZ was higher in tablets containing lactose compared to DPD tablets (even in the acidic medium), this example demonstrates the complex interactions between formulation components and their potential to alter dissolution behaviour in the different gastrointestinal compartments.

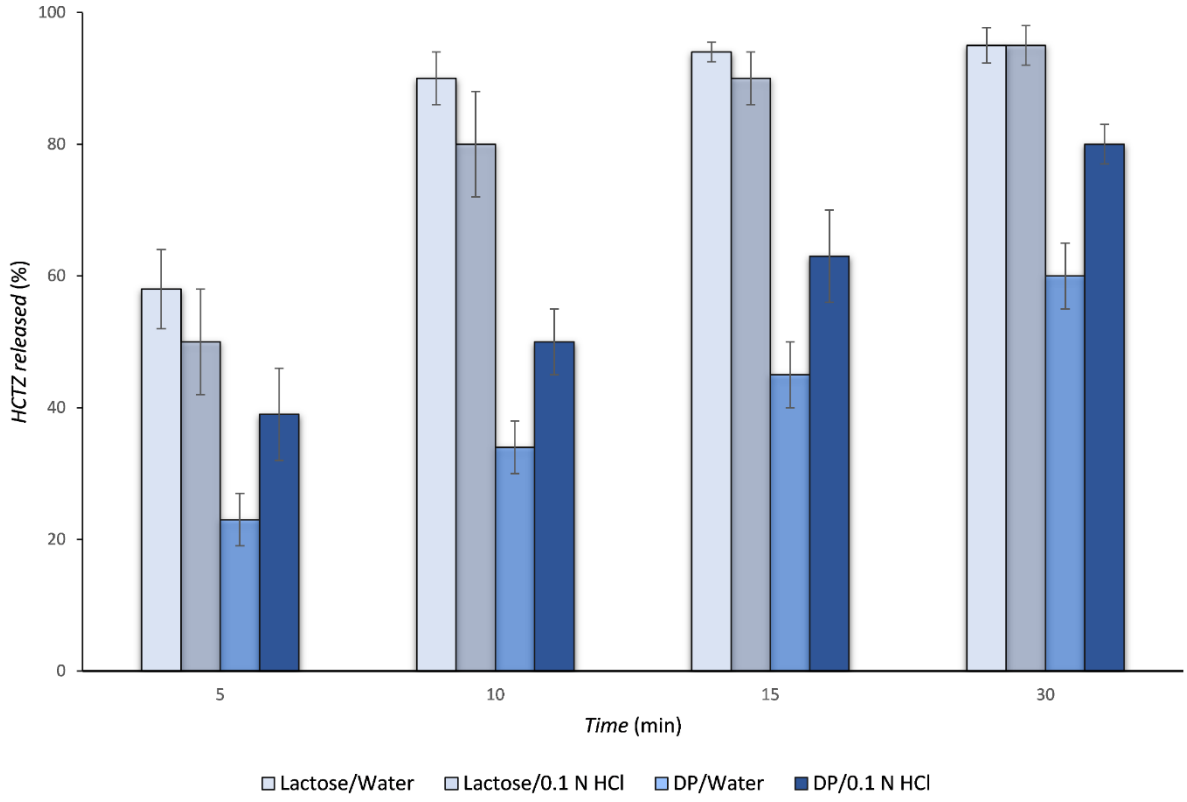

Figure 1.2: % HCTZ release versus time from tablets containing A: Croscarmellose sodium and Lactose in i. water (light grey bars) and ii. 0.1N HCl (dark grey bars) B: Croscarmellose sodium and Dicalcium Phosphate (DP) in i. water (light blue bars) and ii. 0.1N HCl (dark blue bars) (mean ±SD, n=6). [modified from [65]]

1.5.2 Binders

Binders are typically used in solid dosage form manufacturing to promote adequate mechanical strength of granules or tablets. Wet binders are used in wet granulation to ensure appropriate granule formation with good flow properties while dry binders are incorporated after the granulation step or in direct compression to facilitate compaction and formation of strong tablets. Commonly used binders include: disaccharides, starches, celluloses and synthetic polymers (polyvinylpyrrolidone, polyethylene glycol).

1.5.2.1 Microcrystalline Cellulose

Cellulose is a polysaccharide composed by β (1→4) linked D-glucose units forming microfibrils in plant cells (**Figure 1.3**).

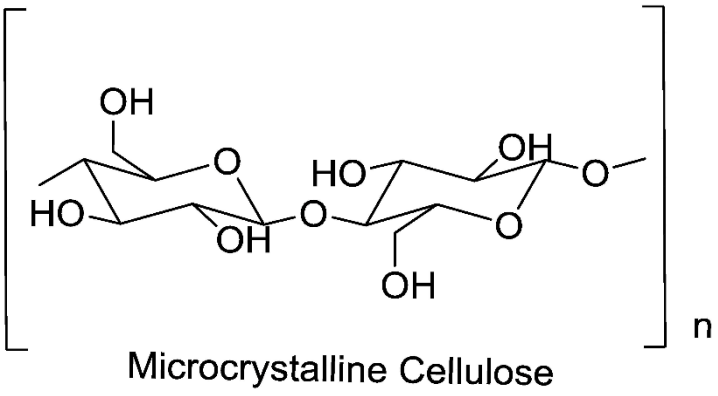

Figure 1.3: Chemical structure of Microcrystalline Cellulose (ChemDraw Professional 15.0).

These microfibrils bond together to create large crystalline regions with intervened amorphous parts. Microcrystalline cellulose (MCC) is obtained by hydrolytic depolymerisation of cellulose in order to isolate the crystalline regions with, usually, a subsequent spray drying step to obtain dry and porous particles [66]. Cellulose for MCC production is mainly derived from wood. Different grades of MCC with a variety of particle size/particle size distribution, moisture content and bulk density are available in the market.

MCC is mainly used as a binder/filler in tablet manufacturing, with good disintegrant and lubricant properties. Its functionality as a binder relates to its ability to deform when compression force is applied. MCC particles come in closer contact and form multiple hydrogen bonds leading to strong compacts. Potential critical material properties of MCC with respect to its functionality as a binder include: moisture content, particle size, bulk density, specific surface area, degree of polymerization and crystallinity [4].

Molecular Properties

The degree of polymerization may affect tabletability, with highly polymerized MCC molecules leading to powders with small particle size and smooth surface. These attributes impact flowability (finer fibers with increased adhesiveness) but have a positive effect on tablet hardness. Tablets containing MCC with a degree of polymerization of 244 and 299 were twice as strong as those produced with an MCC with a degree of polymerization of 199 [67]. In general, degrees of polymerization

favoring the fibrous structure of the polymer, improve tabletability but compromise powder flowability [4]. Impurities in MCC brands can affect drug stability (hydrolysis, drug adsorption onto the polymer) [49].

Structural Properties

Two MCC polymorphs, MCC I and MCC II, differing on the hydrogen bonding between the microfibrils (parallel and anti-parallel orientation of the MCC chain, respectively) have been described. Powder properties of the two polymorphs show great variation and a twofold difference of the swelling value of the two polymorphs is observed (0.2 mL/g for MCC I vs 0.8 mL/g for MCC II) leading to rapid disintegration of MCC II due to the higher water uptake [68]. The degree of crystallinity/amorphicity has a similar pattern, and the presence of amorphous regions in MCC affects water penetration that could affect tablet dissolution. MCC undergoing an extra grinding step to reduce crystallinity and generate amorphous structures led to an increase in water penetration owned to hydrogen bonding between the amorphous regions and water [69]. MCC crystallinity has an impact on dissolution, as an increase in water penetration is noted with lower MCC crystallinity. A decrease of the dissolution rate of acetaminophen tablet as MCC crystallinity decreased from 65.5% to 37.6% and subsequent increase of the dissolution rate as the degree of MCC crystallinity was further reduced (25.8% to 12.1%) has been reported [70]. These studies suggest that the crystallinity of MCC could be a critical material attribute that should be examined with respect to dissolution.

Particle Properties

Particle properties impact tablet hardness and dissolution. A decrease in particle size of MCC would increase cohesiveness resulting in production of stronger tablets after compression. A 32 μm decrease in MCC particle size (d_{50}) showed a statistically significant increase in disintegration time of tablets containing otanabant (BCS Class IV drug), spray dried lactose and magnesium stearate [51]. Porosity affects disintegration/dissolution, with water penetration in plain MCC tablets of 15% nominal porosity to be achieved in 19 s compared to 148 s needed for 5% porosity tablets [71].

Level

When MCC is incorporated into solid dosage forms as a binder/diluent, it typically comprises the 20-90% w/w of the tablet [66]. High MCC concentrations, may greatly increase tablet hardness leading to problematic disintegration and dissolution. For this reason when microcrystalline cellulose is used as a binder, inclusion of a disintegrant is recommended to achieve adequate disintegration and dissolution. As a polymer, MCC tends to swell in aqueous solution, with swelling values of 0.2 mL/g and 0.8 mL/g for MCC I and MCC II, respectively [68]. In high MCC concentrations, the increased viscous layer, caused by swelling, will potentially affect drug release.

Biopharmaceutical Properties

Changing the temperature of the dissolution medium affects MCC functionality. Increasing the temperature of the dissolution medium (water; from 20 °C to 37 °C) resulted in faster swelling and water transport in plain MCC tablets, even though, full disintegration did not occur throughout the duration of the experiment at both temperatures [71]. Information related to other biopharmaceutical properties of MCC have not been reported.

1.5.2.2 Hypromellose

Hypromellose, also called hydroxylpropyl methylcellulose (HPMC), is a water soluble nonionic cellulosic polymer substituted with methoxy and hydroxypropyl groups (**Figure 1.4**).

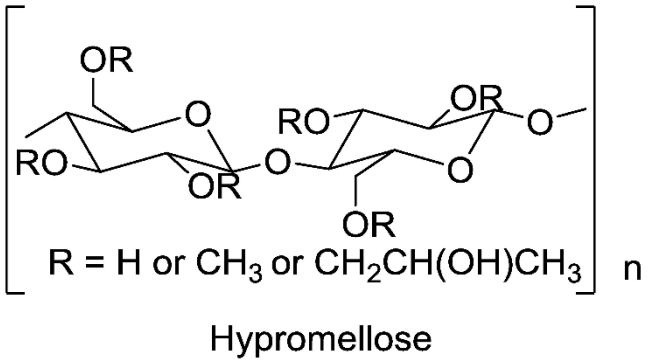

Figure 1.4: Chemical structure of Hypromellose (ChemDraw Professional 15.0).

HPMC is manufactured by chemical modification of cotton or wood derived cellulose. It is used as a wet granulation or dry binder and as a rate controlling release polymer in extended release formulations [72]. The effectiveness of HPMC as a release modifier is advantageous in reducing dosage frequency and sustaining drug blood levels. But it can compromise drug dissolution when used as a binder, where controlled release is not necessary expected, as upon contact with aqueous solutions, the polymer hydrates and forms a viscous gel layer which is thickened when more water penetrates. As the polymer becomes fully hydrated, it tends to relax and dissolve, in a process called erosion [73]. Drug release when HPMC forms this viscous layer consists of three processes: dissolution in the matrix, diffusion through the gel layer and delivery of the drug in the medium as the polymer erodes [74]. Different grades of HPMC are available in the market according to particle size distribution, viscosity and methoxy:hydroxypropoxyl substitution. These characteristics of HPMC along with its particle size affect the functionality of the excipient.

Molecular Properties

The degree of polymerization and substitution are critical aspects for HPMC performance. Molecular weight and chain length have a direct effect on the viscosity of HPMC aqueous solutions. H-bonding between oxygen atoms in ether groups and water molecules leads to extension of the polymer and formation of a coiled shaped structure. Coiled polymers tend to form more H-bonds, entrap water and form entanglements with other coiled molecules resulting in increased resistance to flow. Therefore, polymers with high molecular weight tend to swell faster and form viscous layers. The gel layer thickness increases with increased molecular weight while erosion of the layer is decreased [75]. A counter effect of HPMC molecular weight on gel formation has been reported. Increased molecular weight results in improved swelling properties but reduces water penetration, as the high number of entanglements lead to a less porous layer [76]. Since water penetration affects drug release and dissolution, HPMC molecular weight could be considered as a critical material property whose variation impacts release and dissolution. When three differently substituted HPMC grades were used in acetazolamide (poorly soluble drug) tablet (HPMC 2910, HMPC 2208, HPMC 2906; the first two digits indicate the % methoxy groups and the two last digits the % of hydroxypropyl group) a decrease in

drug release was found with a rank order HPMC 2910> HPMC 2208> HPMC 2906 [77]. Not only the hydroxypropyl content and the degree of substitution but also the substitution pattern affects release and dissolution. Heterogeneity in substitution pattern alters the release of the polymer due to hydrophobic interactions between the substituents [78] with an expected subsequent drug release alteration [79]. Variation in substitution pattern causes batch to batch variability and sourcing from different suppliers should be evaluated [80].

Particle Properties

Particle size affects drug release and dissolution through its impact on tablet hardness and water penetration. HPMC of small particle size form stronger tablets due to increased surface area and interparticle cohesiveness, whereas HPMC of larger particles trigger rapid dissolution, as they do not fully occupy space around particles leaving voids for water penetration [81]. HPMC particle sizes above 113 μm increased dissolution rate of aspirin [82]. Drug release was caused by: disintegration for large particle sizes, diffusion for medium sizes and a combination of diffusion and erosion for smaller particle sizes. These effects were attributed to the proximity of polymer particles and the differences in the porosity of the formed hydrogel [82].

Level

The impact of HPMC properties on dissolution depends on the amount of HPMC in the formulation. When used as a binder, HPMC is added in a level of 2-5% w/w [72]. Direct impact of HPMC concentrations on dissolution has been reported for levels >10 % w/w [83]. The level of the polymer makes solid formulations more prone to particle size variation. The faster dissolution observed with higher HPMC particle sizes due to their porous arrangement [81], is annihilated in high concentrations as more polymer chains are present leaving no spaces for water penetration [81].

Biopharmaceutical properties

From a biopharmaceutical perspective, ionic strength, composition of dissolution medium and presence of food are likely to affect HPMC performance. The presence of salts in the medium affect the hydration of the polymer. Some salts, cause polymer dehydration dependent on salt's affinity to water of hydration (salting-in/salting-out effect) and subsequent loss of gel uniformity leading to inconsistent drug

release [84]. NaCl interacts with water and affects the sol-gel formation (thermo-reversible gelation of aqueous polymeric solutions) of HPMC [85]. In an aqueous HPMC solution, the hydroxyl groups of the polymer interact with water through hydrogen bonding. Upon heating, these bonds are disrupted leaving the hydrophobic parts of the polymer exposed to interact with each other with subsequent formation of a gel. Increasing NaCl concentrations (0-0.8 M), as salting out ion, shifts this thermogelation to lower temperatures [85]. Presence of salts in high concentrations will affect gel layer formation and can lead to burst drug release [86]. Low salt concentrations impede polymer erosion, which is more pronounced in low viscosity grade polymers·[87], leading to decreased drug dissolution. Implications caused by the heterogeneity in the gastrointestinal physiological conditions {gastric (35mM NaCl) and intestinal contents (100 mM NaCl) and fasted and fed state conditions [88]} are expected.

The behavior of cellulosic polymers can be strongly related to physiological temperature. In an intersupplier comparison of HPC batches, differences in dissolution rate of HCTZ tablets were reported and attributed to HPC solubility and its cloud point. The cloud point, that is the temperature above which a polymer solution becomes turbid, relates to polymer's hydrophilicity with less hydrophilic polymers undergoing this transition in lower temperatures, and a less viscous layer is formed in temperatures above it. Therefore, when the HPC brand with a cloud point closer to 37°C was used, faster dissolution of HCTZ from the tablet formulation was observed [89]. Since HPC and HPMC are included in the same polymeric class possessing comparable functionality and properties, a similar behavior is expected for HPMC.

Meal components, such as sugars and fat, interact with HPMC affecting its biopharmaceutical properties. The same ionic effect on HPMC dehydration pattern, has been found for dietary sugars. Dietary sugars cause dehydration of the polymer according to their structure and lactose is one of the most potent disaccharides in inducing HPMC dehydration even in low concentration (0.5 M) [90]. In low sugar concentrations, the decreased erosion leads to thicker gel layers that delay drug diffusion and release on the medium, whereas in higher concentrations, the suppression of the gel formation leads to rapid drug release [90]. The presence of milk reduced caffeine release from tablets containing HPMC. High fat concentrations,

relevant to fat content of the medium, were deposited on these tablets at the early stages of gel formation, and the fat layer was still present at later time points. Possible coalescence between fat droplets and phase separation of these lipidic compositions on the formed gel resulted in reduced drug release [91, 92] Furthermore, hydrodynamics of the dissolution apparatus permitted a better understanding of the effect of milk on the release from these tablets containing HPMC. With the flow through cell apparatus the decrease in dissolution rate is more pronounced due to the absence of erosional forces and occurs in lower fat contents than in the basket apparatus [91]. These findings suggest that the fed state affects the release from formulations containing HPMC. Biorelevant dissolution testing could shed light on the complex effect of physiological conditions on excipient functionality and release/dissolution.

Dissolution of low and high viscosity grade HPMC in phosphate buffer pH 6.8 studied with surface dissolution UV-imaging revealed that for both grades the gel layer was formed rapidly within 15 minutes. For the low viscosity polymer, the initial high concentrations decreased as the polymer expanded. Then, the gel layer was stabilized from the dissolution of undissolved particles (that contribute to the increased polymer concentrations in close proximity to the sample). As the polymer expanded, its concentration was decreased due to polymer disentanglement forming the diffusion layer and the polymer was completely dissolved and diffused in the bulk (**Figure 1.5a**). HPMC of higher viscosity showed increased concentrations in the gel layer but decreased rate of diffusion and dissolution (**Figure 1.5c**). When agitation was applied, a thinner layer with lower HPMC concentrations and slow diffusion rate were observed (**Figure 1.5b**). The effect of agitation was more pronounced for the low viscosity HPMC, as it was more sensitive to shear force (**Figure 1.5d**) [74].

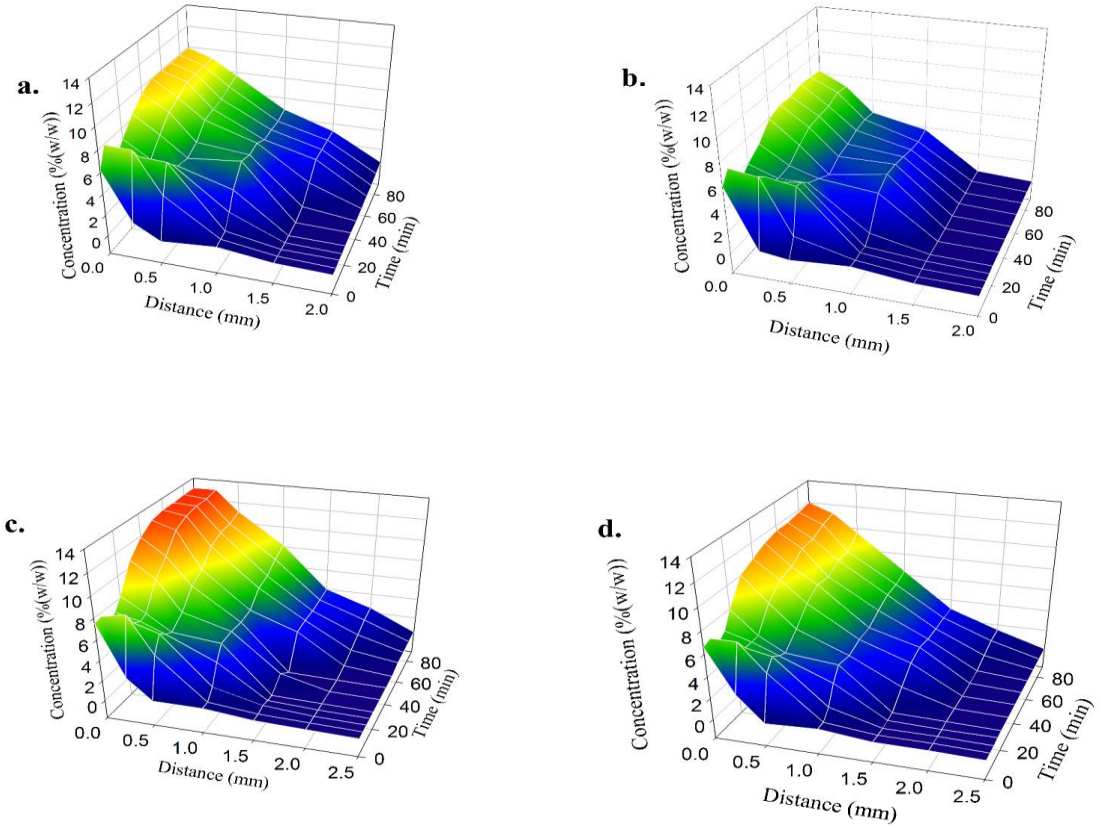

Figure 1.5: % released vs time and distance from the sample of HPMC 15 cP in stagnant (a.) and 0.5mL/min flow rate (b.) and HPMC 50 cP in stagnant (c.) and 0.5mL/min flow rate (d.) in phosphate buffer (pH 6.8) with UV dissolution imaging (SigmaPlot 13.0). [modified from [74]

1.5.3 Lubricants

Lubricants are used in solid dosage forms manufacture to enhance processability of intermediate blends and tablets. Friction or cohesiveness between particles impose a barrier in powder or tablet flowability affecting content uniformity, compaction, tablet hardness and therefore product performance. Lubricants address flowability issues, by adherence to die or particle surfaces and reduction of friction or cohesiveness leading to adequate flow properties. Lubrication involves the creation of a film between surfaces or interfaces in order to reduce cohesion between particles or adhesion of particles onto surfaces [93]. The most commonly used lubricants include stearates (magnesium, calcium, sodium), talc, waxes and sodium lauryl sulfate. Magnesium stearate properties and behavior are reviewed as it possesses excellent lubricant properties.

1.5.3.1 Magnesium Stearate

Magnesium Stearate, a salt containing two equivalents of a fatty acid (usually stearic and palmitic acid) and a charged magnesium, is manufactured by a reaction between fatty acid salts and inorganic salts (**Figure 1.6**) [94].

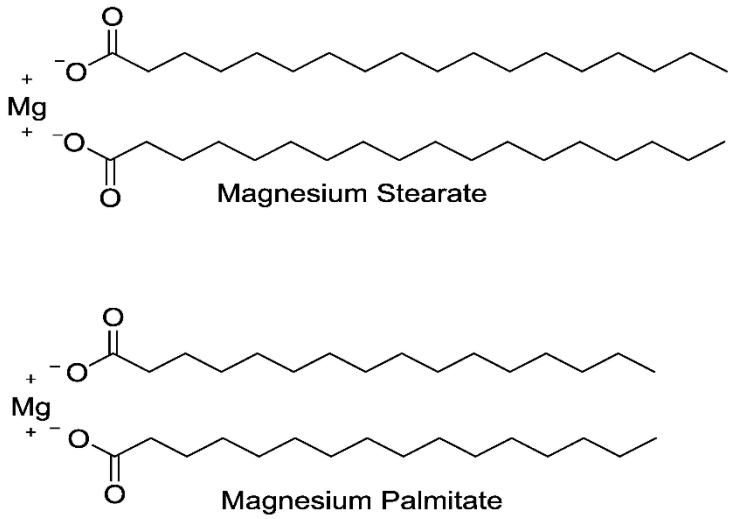

Figure 1.6: Chemical structure of Magnesium Stearate and Magnesium Palmitate (ChemDraw Professional 15.0)

Fatty acids can be bovine or vegetable-derived [95]. Its lubricant effect relates to the adherence of the polar moiety on granules or powders while the lipophilic part is oriented away from the particle's surface [96]. Its ability to form a waxy layer around particles and tablets leads to reduced water penetration and dissolution can be compromised due to its hydrophobicity. Lubrication efficiency and dissolution, are inversely related as over-lubrication decreases dissolution rate.

Molecular Properties

A maximum of 4-5% in magnesium weight fraction and a minimum of 40% in stearic acid weight fraction is described in the USP [97]. Magnesium stearate is a mixture of stearic and palmitic salts. The sum of stearic and palmitic acid should encounter for the 90% of total weight fraction [98], but the exact ratio of the stearic (C-18) and palmitic (C-16) acid, composing the commercial magnesium stearate, is not set in the Pharmacopoeia specifications.

Depending on the manufacturing process and humidity, four different hydrates of magnesium stearate can be formed (anhydrate, monohydrate, dihydrate, trihydrate), leading to different crystal habits with altered functionality [99]. When preparing magnesium stearate with a precipitation method, precipitation in pH 9 leads to the formation of the dihydrate form, while precipitation in pH 7 or 11 leads to a lower hydration state [100].

Structural Properties

The different crystal structures identified for the different magnesium stearate hydrates include the plate-shaped structure for the dihydrate and needle-shaped structure for the monohydrate and trihydrate form [100-102]. This difference in shape is attributed to a change in the angle of inclination of the hydrocarbon chain caused by the addition of the water molecule [100]. The different crystalline forms have an effect on the magnesium stearate functionality as an excipient. The monohydrate form produces tablets with lower variability during tablet manufacturing [99]. The dihydrate form acts as better lubricant due to its lamellar shape as it shears readily under applied tangential forces [101, 103, 104] and has a lower tendency to cause over-lubrication [99]. The irregularity of commercial magnesium stearate shape, compared to high purity magnesium stearate and palmitate, relates to reduced lubricant properties [104].

Particle Properties

Surface area (SA) and particle size affect magnesium stearate functionality. Increasing the SA of the lubricant (due to particle size reduction) leads to higher adhesion work and a thin homogeneous layer on particle surface, whereas decreasing SA results in enrichment of the surface with lubricant particles [96]. Larger particles have less tendency to strongly adhere to particle surfaces leading to less uniform coats. In both cases, (strong or thick layer) water will face difficulties in penetrating this layer. The high coverage of particle surfaces with the lubricant during blending reduces interparticle bonding leading to weakened tablets [105]. Investigation of the optimum particle size/SA of magnesium stearate, without compromising any quality attributes, is needed as the two extreme levels both may have a negative impact on drug release.

Level

Since magnesium stearate is hydrophobic care should be taken when added in solid dosage forms as it can compromise drug release. The amount and the mixing time of magnesium stearate in the formulation are critical dissolution variables; increased levels and longer mixing time reduces drug dissolution from capsules [94]. A range of 0.25-5.0% w/w magnesium stearate is used in drug product development [94]. Increasing magnesium stearate level (0.25%-1.0%-5.0% w/w) decreased indomethacin dissolution, due to the decreased interfacial area between the dissolution medium (acetate buffer pH 5 with 0.1% w/v sodium lauryl sulphate) and the drug [106]. Mechanofusion, a process used to coat particles with fine materials, has been found beneficial for drug dissolution, as coated particles with magnesium stearate exhibited decreased agglomeration and enhanced dissolution [107]. In the case of mechanofused magnesium stearate-coated indomethacin powder, drug dissolution was enhanced only in the early stages of dissolution, and dissolution reached a plateau (~80% drug dissolved) at later stages with slightly higher concentrations achieved only for the 0.25 and 1% w/w magnesium stearate [106].

1.5.4 Superdisintegrants

Disintegration is needed in immediate release dosage forms where quick onset of action is desired. A single or a combination of mechanisms have been proposed for the disintegration of solid formulations. Firstly, swelling of the disintegrant can compensate the adhesion forces of other formulation components, causing the tablet fragmentation. Furthermore, the porous structure of several disintegrants and their ability to absorb water via capillary action (wicking) is a potential mechanism for their action. Finally, fragmentation of tablets can be caused from elastic deformation of disintegrants under pressure and release of high energy upon exposure to water due to the ability of particles to recover their initial structure [108]. Common disintegrants used in solid formulations include: starches and modified starches. The introduction of low concentrations of superdisintegrants as agents providing disintegration within few minutes is optimistic in terms of drug delivery in enhancing the dissolution rate of solid formulations [109]. The most notable superdisintegrants include crosslinked polymers such as: sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone.

1.5.4.1 Sodium Starch Glycolate

Starch is a polysaccharide consisted of amylose and amylopectin, and can be extracted and processed for pharmaceutical use by several plants including maize, potato, rice, corn. Starch modification can be performed in order to improve its functionality as disintegrant. SSG is the sodium salt of the carboxymethyl ether of starch (**Figure 1.7**).

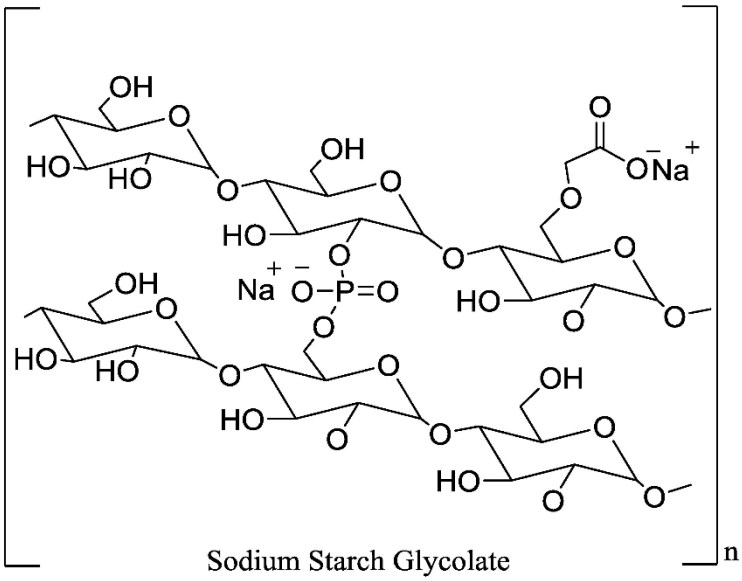

Figure 1.7*:* Chemical structure of crosslinked Sodium Starch Glycolate (ChemDraw Professional 15.0).

SSG derives from starch (from several sources) after two chemical modification processes: substitution to increase hydrophilicity and cross-linking to reduce solubility and gel formation upon contact with water [110]. It is used in pharmaceutical manufacturing as a superdisintegrant as it acts through rapid swelling due to the absorption of large amounts of water leading to fast disintegration [111]. The functional mechanism of SSG was revealed by High-Resolution Real-Time Magnetic Resonance Imaging (MRI) through investigation of the direction to which the tablet expands when disintegration occurs. SSG acts through swelling as an omni-directional expansion was observed with different grades of SSG [112]. Different grades of SSG are available according to particle size distribution, sodium chloride content and pH.

Molecular Properties

The degree of substitution, due to the role of the carboxymethyl group on functionality, has to be defined. In USP, the amount of sodium in SSG is set between 2.8-4.2%, whereas the degree of substitution is not specified [113]. Values for the degree of substitution between 0.23-0.32 have been reported [114]. Hydration and swelling of SSG leading to fast tablet disintegration, relate to degree of substitution. An increase in swelling and water uptake observed as substitution increases from 0.20 to 0.29 and the opposite effects at higher substitution. An optimum degree of substitution value between 0.28-0.29 for faster and higher dissolution of aspirin tablets was reported [115]. A higher degree of substitution can lead to increased drug-excipient interactions as weakly basic drugs can be absorbed onto the polymer [49] Crosslinking in SSG, achieved through the phosphate group, leads to a high spacing between SSG chains facilitates water penetration and swelling and reduce gel formation [109]. The extended swelling of SSG compared to other swelling disintegrants is attributed to this type of crosslinking (e.g. croscarmellose is crosslinked through esterification which does not allow this high spacing between the polymer chains). An increase of 25%-35% of crosslinking, leads to powders with increased swelling and water uptake with further increase in crosslinking leading to lower swelling and water uptake. An optimum value at medium levels of crosslinking (33-35%) for dissolution of aspirin tablets has been reported [115].

Particle Properties

Particle size affects disintegrant functionality of SSG, with larger particles being more efficient [110]. An approximate threefold increase in particle size of SSG resulted in a proportional decrease in disintegration time [116]. It can be speculated though that in the case of super-disintegrants, it is questionable whether a change in the second disintegration time-scale can have a direct major impact on dissolution. An indirect effect of the particle size on dissolution is more likely to be expected through its effect on solution's viscosity. As the particle size of polymers decreases, a more viscous layer is formed due to increased interaction with water, creating a barrier for drug diffusion and leading to delayed dissolution

Level

Typical amount of SSG used in drug formulation ranges between 2%-8% w/w [117]. Low SSG levels (0.25%, 0.5% and 1% w/w) in paracetamol tablets resulted in

long and varied disintegration times (60min, 40min, 2-15 min, respectively), whereas at higher SSG levels (2% and 4% w/w) the disintegration time was consistent within one minute [115]. SSG in higher levels (>8% of tablet weight) causes an increase in disintegration time due to the formation of a viscous layer which hinders water penetration in the formulation, irrespective of the API solubility [111].

Biopharmaceutical Properties

The pH of the medium affects SSG functionality [65]. SSG hydrates as the anionic carboxyl group interacts with water [65]. In low pH, the polymer gains its neutral form and a less extended interaction with water is expected [65]. In simulated gastric media (0.1 N HCl, pH=1) an approximate twofold reduction in the swelling value and the water uptake of SSG was observed compared to the values in intestinal media (phosphate buffer, pH=6.8) (**Figure 1.8**). Compacts of SSG with spironolactone, filler and lubricant did not show this variation in water sorption in the two media, a fact attributed to the crystallinity of the polymer and the reduced water accessibility when particles are consolidated in strong compacts [109].

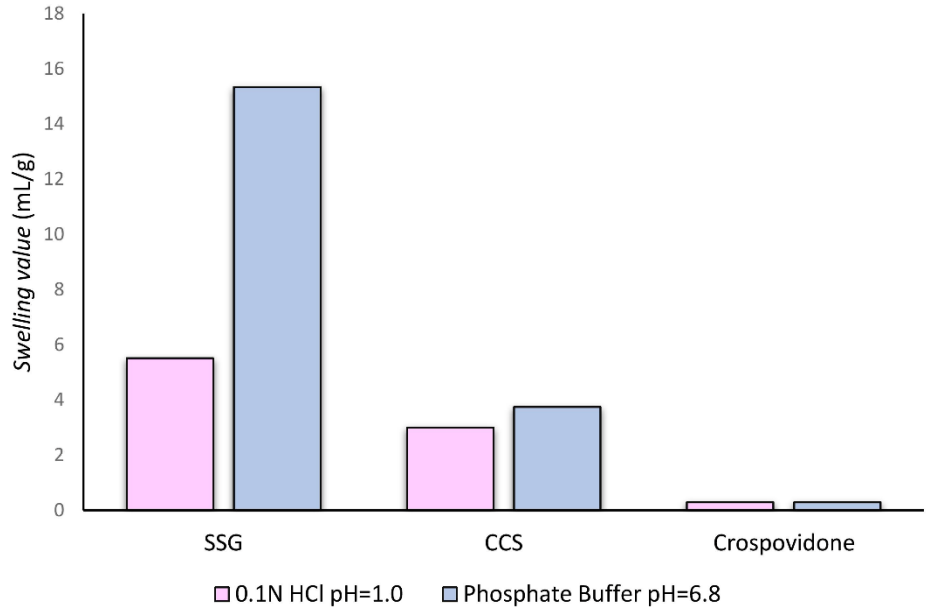

Figure 1.8: Swelling values of SSG, CCS and crospovidone after 20 minutes dispersion of 500 mg of each superdisintegrant in 10 mL of 0.1N HCl (pH=1) (i.) and phosphate buffer (pH=6.8) (ii.) at room temperature. [modified from [109]]

1.5.4.2 Croscarmellose sodium

CCS is a cross-linked polymer of carboxy methylcellulose. Wood or cotton-derived cellulose reacts with sodium hydroxide and sodium monochloroacetate to produce the carboxyl methyl cellulose in a degree of substitution of 0.7. The excess of monochloroacetate hydrolyzes to glycolic acid which reacts with the sodium carboxy methyl group of the polymer and catalyzes the esterification of this group with the closest polymer chains leading to the formation of crosslinks (**Figure 1.9**) [118].

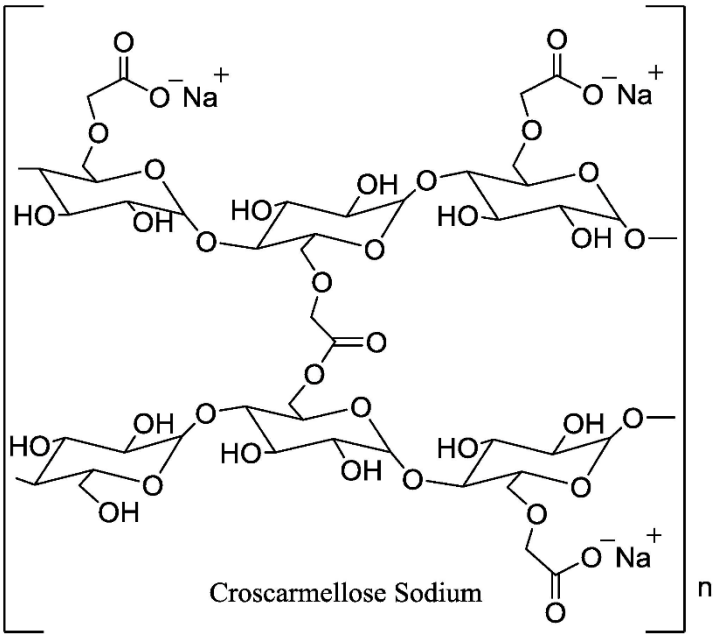

Figure 1.9: Chemical structure of Croscarmellose sodium (ChemDraw Professional 15.0).

It is used in tablet or capsule manufacturing as a super disintegrant acting mainly through a combination of swelling and wicking. The swelling mechanism of CCS was confirmed by MRI studies, as tablets containing CCS expanded in an omni-directional way [112]. At initial stages, disintegration depended on tablet density and water penetration was reduced as tablet hardness was increased. At later stages, as the polymer swells, new pores were formed and water uptake was no longer related to tablet density. Stronger solid dosage forms resulted in better disintegration, as their less porous structure caused a greater swelling force to be exerted on tablets and formation of widen pores that facilitate water penetration [112].

Molecular Properties

As swelling of CCS is attributed to the hydration of the carboxy methyl group, the degree of substitution defines CCS functionality. Degree of substitution refers to the total acidic (acid form) and basic (sodium salt) components of superdisintegrants. The basic substituent (level of salt) correlates CCS disintegration to the pH of the medium, as CCS turns to its acidic form on low pH with a subsequent loss of its swelling ability [119]. Measuring the volume median diameter gave higher values for CCS in water compared to HCl 0.1 N [65], indicating a more efficient swelling of the sodium salt than the free acid due to higher hydrophilicity. Acid/base ratio and total degree of substitution vary along different CCS brands. Brands with higher basic substituents exhibit larger settling volumes and higher maximal water uptake and size increase. Variation in disintegration times can be attributed to differences in composition when all other properties, such as particle size are similar [119]. A higher degree of substitution may induce drug-excipient interactions. Exposure of delavirdine mesylate tablets containing CCS to high humidity (40 °C, 75% RH) for 8 weeks led to a decrease in drug's dissolution probably from the conversion of delavirdine to its free basic form due to an interaction between the carboxyl group of the polymer and methanosulfonic acid [120].

Particle Properties

For croscarmellose, as a swelling polymer, a larger particle size is expected to lead to enhanced swelling and fast disintegration. Brands of higher particle size of different croscarmellose suppliers showed increased settling volumes and water uptake [119]. An optimum particle size has not been reported. Since, croscarmellose forms a viscous layer upon contact with water, it should be expected that the notion that smaller particles sizes will form a more viscous layer due to enhanced interactions with water would be applicable

Level

In tablet formulations, CCS is used at 0.5%-5.0% w/w to promote fast disintegration [118]. As CCS swells upon contact with water, an increase in its fraction results in the formation of a viscous gel layer acting as a barrier for product disintegration. For aspirin, ascorbic acid and ibuprofen tablets, an optimal superdisintegrant concentration of 7% of the tablet weight was reported to give best disintegration values and up to this level, disintegration time increased irrespective of

drug solubility [111]. Even if the difference in disintegration time is low, dissolution can be greatly affected as the drug will have to diffuse through the viscous disintegrant layer.

Biopharmaceutical Properties

Since CCS is a sodium salt, the pH of the medium affects its ionization. In acidic medium, CCS turns to its neutral form with decreased hydrating and swelling capacity [65], but to lesser extent than the highly swelling SSG (section 1.5.4.1.) (**Figure 1.8**) [109]. Therefore, the functional profile of CCS in the stomach and small intestine is expected to be different. Investigation of the effect of composition and level in solid formulations of CCS on solid dosage form disintegration and dissolution based on biorelevant approaches would provide an insight on implications for its in vivo functionality. CCS may impact drug's permeability as it binds to Ca^{2+} cations and compromises tight junction integrity; an increased ranitidine permeability in the presence of CCS has been reported [121].

1.5.4.3 Crospovidone

Crospovidone is a water-insoluble nonionic polymer consisted of cross-linked 1-vinyl-2-pyrrolidone monomers (**Figure 1.10**).

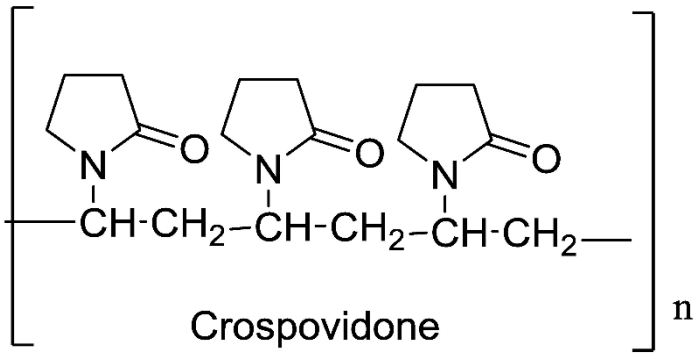

Figure 1.10: Chemical structure of Crospovidone (ChemDraw Professional 15.

It is manufactured through a popcorn polymerization technique (proliferous polymerization) of the initial monomer leading to the formation of porous particles [122]. Crospovidone, used in solid dosage form manufacturing as a disintegrant, acts via a different mechanism than the swelling starches. When compaction force is applied, the polymer deforms. Upon contact with water, it absorbs water via capillary

action and regains its normal structure releasing an amount of energy capable to break the tablet. This shape recovery was confirmed with MRI as a uni-directional expansion of tablet was observed [112]. Crospovidone is considered an excellent excipient leading to fast disintegration without compromising dissolution due to its inability to form a gel [123]. Several grades of crospovidone are available on market differing in particle size distribution (standard, fine, superfine or micronized powder), bulk density, hydration capacity and peroxide specifications.

Molecular Properties

Crospovidone is not substituted and lacks ionizable groups. Therefore, molecular properties of crospovidone are unlikely to affect excipient's functionality. Residual peroxides, though, in crospovidone may affect the stability of oxygen sensitive drugs [49].

Particle Properties

Monographs define crospovidone into two broad particle size types: A (coarser than 50 μm) and B (finer than 50μm) [124]. For crospovidone, a wicking agent, particle size relates to particle porosity. As size increases, the intraparticular porosity increases as well leading to larger water uptake and faster disintegration [125]. A more thorough consideration of crospovidone particle size specifications could be beneficial. Two equivalent grades of crospovidone powder (Polyplasdone XL and Kollidon CL) with the same particle size distribution from different suppliers showed differences in particle porosity and water uptake. When dicalcium phosphate dihydrate was incorporated in HCTZ tablets, the grade with the higher porosity (Polyplasdone XL) dissolved 33% of the drug in 15 minutes while its equivalent (Kollidon CL) released only 18% in the same time. When Kollidon CL (low porosity crospovidone grade) was compared to a grade of lower particle size from the first supplier (Polyplasdone XL 10), the latter showed increased liquid uptake and greater HCTZ dissolution than the former [125]. Whether this behavior relates to differences in particle size or variation in production processes, it designates that equivalent grades according to monograph specifications may have different functionality and interchange between them should be avoided.

Level

Common levels of crospovidone used in solid dosage forms to provide fast disintegration are 2%-5% w/w [126]. The disintegration time of tablets containing highly soluble drugs (aspirin and ascorbic acid) and crospovidone decreased until a maximum crospovidone level of 8% of tablet weight. Levels higher than 8% w/w led to increased disintegration time. When ibuprofen, a poorly soluble drug, was formulated with crospovidone in tablet, disintegration time was at its lowest value (30 s) at 8% of tablet weight with no subsequent increase with increased crospovidone level due to a possible effect of crospovidone concentration on tablet hardness. Crospovidone levels higher than 8% of tablet weight produce weaker tablets that disintegrate faster [111]. The effect of crospovidone on tablet hardness and its relation to disintegration should be further investigated.

Biopharmaceutical Properties

pH is unlikely to affect crospovidone functionality, as it is a nonionic non gelling polymer [65]. The swelling values were found 0.50 mL/g in simulated gastric (0.1 N HCl, pH=1) and intestinal (phosphate buffer, pH=6.8) media (**Figure 1.8**) due to the absence of ionization and the low swelling ability of crospovidone [109]. Water uptake of disintegrant powder was different in the two media, with values of 0.32 g/s and 0.52 g/s in the gastric and the intestinal media, respectively, due to a potential uncoiling of the chain in acidic medium [109]. This difference, though, was annihilated in compacts containing spironolactone, diluent-binder, disintegrant and lubricant and water sorption of these formulations was unaffected by the different pH. Disintegration times were higher (500 s and 350 s in 0.1 N HCl pH 1 and phosphate buffer pH 6.8, respectively) for lubricated compacts (with magnesium stearate) when compared to the unlubricated ones (150 s in both media). For lubricated compacts, higher disintegration time was observed in gastric media than in intestinal media because of the combination of uncoiled crospovidone chains and reduced water penetration caused by the hydrophobic lubricant [109].

1.6. Conclusions

Excipients constitute a major component of solid dosage forms and their use covers a variety of functions, from dosage manufacturing to dosage performance. Their importance as potential causes for final product variability is recognized and efforts in characterizing their critical material attributes have been made. Despite the

rising awareness on excipient variability, few reports have addressed their role in drug product dissolution. Examining dissolution inconsistencies is essential, since *in vitro* dissolution testing constitutes a predictive tool of *in vivo* performance apart from its role in quality control testing. In this review, potential critical material attributes of commonly used excipients have been discussed with respect to product performance. Criticality is related to excipient functionality that can be altered according to product components and physiological conditions. A great effort still needs to be made to delineate the complex effects of physiological factors on product performance. We conclude that, despite the challenges imposed, an investigation of the exact excipient mechanisms in drug release is of paramount importance in order to adequately characterize and optimize excipient properties by incorporating the QbD principles.

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Chapter 1 Commentary

With the introduction of the Quality by Design (QbD) initiative in the pharmaceutical industry, the critical factors affecting final product quality need to be identified, understood and controlled. The presence of excipients as major components in solid oral dosage forms can be challenging for the performance of final products. Excipient variability caused by different natural sources, changes in excipient manufacturing processes or the inadequate specifications posed by regulatory agencies complicates this issue. It follows that approaches to understand and implement excipient variability in the QbD concept are needed for the production of robust pharmaceutical formulations. The biopharmaceutical implications of excipients on product performance need also to be considered in current methodologies as excipients can affect or be affected by the heterogeneous composition of the gastrointestinal lumen both *in vitro* and *in vivo*. The molecular, structural, particle properties and level of commonly used excipients in immediate release formulations (diluents, binders, lubricants, superdisintegrants) that could affect product performance were presented in this chapter. The biopharmaceutical implications of excipients on drug dissolution were, as well, considered and demonstrated the necessity to study the role of excipients on oral drug performance in a biorelevant perspective. Based on this analysis, lubricants (magnesium stearate), binders (hypromellose) and superdisintegrants (sodium starch glycolate, croscarmellose sodium, crospovidone) were selected for further experimentation, as their direct impact or unclear mechanistic role on drug dissolution was highlighted.

Chapter 2 Preface

As revealed in Chapter 1, understanding the critical material properties and the biopharmaceutical implications of excipients on drug product performance is beneficial towards the successful implementation of the Quality by Design (QbD) concept in the pharmaceutical development. Lubricants are excipients added in oral solid dosage forms to improve intermediate blend or tablet processing during manufacturing. Magnesium stearate (MgSt) is a frequently used lubricant in immediate release formulations but it can compromise drug dissolution due to its hydrophobic nature. Changes, therefore, in the excipient properties and/or excipient level in formulations could influence the amount of drug dissolved in the gastrointestinal tract and present challenges for oral drug bioavailability. Several excipient critical properties (purity -ratio of stearic and palmitic acid-, crystallinity, particle size distribution (PSD) and specific surface area (SSA)) are known to affect the performance of the excipient and could potentially influence drug dissolution. Moreover, as the varying composition of the gastrointestinal tract can affect the performance of MgSt, *in vitro* methodologies assessing the impact of excipients on product performance need to simulate the *in vivo* conditions. The aim of this chapter is to investigate the impact of MgSt variability and variation on the apparent solubility of drugs with varying physicochemical properties in a biopharmaceutical perspective. The generated data, in combination with results obtained from subsequent chapters, will be used to create a body knowledge of excipient criticality (with the use of multivariate data analysis and the construction of roadmaps) for oral product performance.

Chapter 2. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties. Case study: Magnesium Stearate

Abstract

Presence of excipients, excipient variability (changes in material attributes) and excipient variation (changes in amount) present a challenge for product performance. Understanding the biopharmaceutical factors affecting excipient performance is recommended for successful implementation of excipient variability on Quality by Design (QbD) approaches. The current study investigated the impact of magnesium stearate (MgSt) variability on the apparent solubility of drugs with a wide range of physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility). Compendial and biorelevant media were used to assess the role of gastrointestinal (GI) conditions on the excipient effects on drug apparent solubility. The lipophilic nature of MgSt decreased the apparent solubility of the majority of compounds. The reduction in the drug apparent solubility was more pronounced for highly soluble and/or highly ionized drugs and in presence of more highly crystalline or smaller particle size MgSt. The use of multivariate data analysis revealed the critical physicochemical factors and the complex nature of excipient variability on the reduction in drug apparent solubility. The construction of a roadmap combining drug physicochemical properties and excipient critical material attributed allowed the identification of the cases where presence of excipient or excipient variability may present risks for oral drug performance.

Keywords: excipient variability, magnesium stearate, drug solubility, physicochemical properties, multivariate data analysis

2.1. Introduction

Excipient variability (changes in material properties) and variation (changes in amount) can affect final product quality leading to batch failures, altered bioavailability and bioinequivalence within products [1, 2]. The need for successful implementation of excipient variability in Quality by Design (QbD) approaches is widely recognized. Excipient variability may present challenges in a biopharmaceutical perspective as presence of excipients may affect drug stability, solubility, permeability and overall product performance [3]. Gastrointestinal factors may affect or be affected by excipient performance in pharmaceutical formulations [4]. Understanding the biopharmaceutical risks of excipient variability would be beneficial towards the development of robust oral solid dosage forms.

Magnesium stearate (MgSt) is a frequently used lubricant in tablet manufacturing due to its excellent properties [5]. Typical excipient levels used in immediate release formulations range between 0.25% w/w – 5% w/w [6]. MgSt can compromise drug release, as it acts as water repellent [7, 8] through the formation of a hydrophobic film around drug particles [9, 10]. MgSt may adhere to metal or powder/granule surfaces by its polar Mg^{2+} [5, 11] while the non-polar fatty acid orients away from the coated surface and is responsible for the negative impact on product performance [11] (**Figure 2.1**). Formation of mono or multiparticulate layers around particles by the non-polar head of MgSt [12, 13] has also been suggested as a coating approach for solid dosage forms.

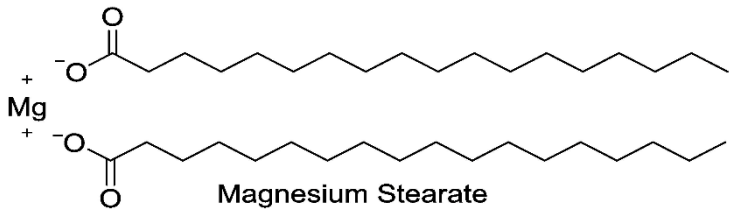


Figure 2.1: Chemical structure of Magnesium Stearate. (ChemDraw Professional 15.0)

MgSt is a mixture of stearic and palmitic salts [4]. Several different hydrates and corresponding solid-state forms of MgSt have been identified: anhydrous, monohydrate (needle – shape or disordered), dihydrate (plate – shape), trihydrate

(needle – shape) [14, 15]. MgSt samples may comprise of crystalline (single or combination of 2 or more forms) or amorphous forms [15]. Molecular, structural, particle properties and excipient level have been identified as potential critical material attributes of MgSt [4]. The purity of MgSt (ratio of stearic and palmitic acid) may affect its lubrication efficiency. The delay in the dissolution of a highly soluble drug (paracetamol, USP 2 apparatus, 0.1 N HCl pH 1, 25 rpm, 37 °C) was more pronounced in the presence of commercial MgSt (pharmaceutical grade mixture of stearic and palmitic salts with not less than 40% of stearic acid) compared to high purity MgSt (> 90% of stearic acid) [9]. The slower drug dissolution was attributed to the formation of an extensive hydrophobic layer around particles by commercial compared to high purity MgSt. The formation of the hydrophobic layer around particles by MgSt depends on the solid-state form of the excipient. Amorphous MgSt hinders the formation of a smooth film around particles due to its irregular shape [16]. Milling crystalline MgSt breaks its crystal structure leading to amorphous material which exhibits poor lubrication efficiency [17]. The significance of the degree of crystallinity (CRS) is highlighted as the negative effects of amorphous MgSt on lubrication can dominate the lubrication efficiency of the crystalline portion [18]. Coating strength and uniformity depend on the particle size distribution (PSD) of the lubricant. Smaller particles create a thin but homogenous layer due to higher adhesion force on surfaces while larger particles have relatively less tendency to adhere on surfaces creating less uniform coats [4]. A statistical evaluation of the factors affecting the lubrication efficiency of MgSt identified that for crystalline MgSt, moisture content, hausner ratio, PSD (d_{50}) and specific surface area (SSA) were critical material properties [18]. Finally, the level of excipient in solid dosage forms may affect the coating efficiency of MgSt and its impact on product performance. Pronounced delay in tablet disintegration and drug dissolution when increasing the amount of MgSt on formulations has been reported as a result of decreased tablet wettability [10].

The biopharmaceutical factors affecting the impact of MgSt on product performance are not fully investigated. The extent at which MgSt delayed drug dissolution was found to depend on the solubility of the active pharmaceutical ingredient (API). Dissolution studies (USP 2 apparatus, 0.1 N HCl pH 1, 75 rpm, 37 °C) of capsules containing drugs of different solubility showed that although MgSt presence delayed drug dissolution, the impact was more pronounced for the drug with

the lowest solubility in the dissolution medium [7]. The pH of the solution will affect the performance of MgSt due to the ionization pattern of the excipient. The dissolution of metformin hydrochloride (USP 2 apparatus, 50 rpm, 37 °C, 900 mL dissolution medium) from tablets containing MgSt was slower in acidic (simulated gastric fluid without pepsin (SGF) pH 1.2) compared to basic conditions (phosphate buffer pH 6.8) [19]. This difference in drug dissolution by MgSt was attributed to the generation of stearic acid in acidic media which causes a more pronounced delay on drug dissolution due to its lower solubility compared to the salt form [19].

The aim of this study was to identify the impact and criticality of MgSt variability and variation on drug apparent solubility from a biopharmaceutical perspective. MgSt variability and variation were assessed by selecting and characterizing three MgSt brands of different grades and/or suppliers to investigate the role of certain critical material attributes including: purity (% of stearic and palmitic acid), CRS (intensity of diffractograms), PSD ($d_{10,}$ $d_{50,}$ d_{90}), excipient level (low: 2% w/w, high: 5% w/w) on drug solubility. The potential biopharmaceutical implications of MgSt variability and variation on drug apparent solubility were investigated by choosing compounds of varying physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and media (compendial and biorelevant) representing the gastric and intestinal conditions. The criticality of certain variables (drug properties, excipient presence, medium characteristics) on the impact of MgSt on drug apparent solubility was examined with the use of multivariate data analysis (Partial Least Squares (PLS)) and the construction of roadmaps.

2.2. Materials and Methods

2.2.1. Materials

APIs: Sulfamethoxazole and paracetamol were obtained from Fisher Scientific (UK). Furosemide, itraconazole and dipyridamole were obtained from VWR (UK). Ibuprofen, carbamazepine and metformin were obtained from Fagron (UK). Excipients: MgSt-BDH was obtained from BDH chemical Ltd (UK). Ligamed MF-2-V and Ligamed MF-3-V were obtained from Peter Greven (Germany). Chemicals: Acetic acid (>99.7%), hydrochloric acid 36.5–38%, HPLC grade methanol, HPLC grade acetonitrile, dichloromethane, heptane, pepsin (from porcine) were obtained from Sigma-Aldrich (UK). Maleic acid, sodium chloride, sodium hydroxide,

potassium phosphate monobasic, sodium dihydrogen orthophosphate dihydrate, disodium hydrogen orthophosphate dihydrate, potassium dihydrogen orthophosphate, anhydrous sodium sulfate, HPLC grade trifluoroacetic acid, stearic acid >98%, palmitic acid >98% were obtained from Fisher Scientific (UK). Boron trifluoride – methanol complex 12% in methanol was obtained from VWR (UK). Sodium taurocholate (Prodotti Chimici Alimentari S.P.A., Italy), egg lecithin – Lipoid EPCS (Lipoid GmbH, Germany), were obtained from the sources specified. Water was ultra-pure (Milli-Q) laboratory grade. Filters: Whatman® 13 mm cellulose nitrate filters 0.45 μm pore size and polytetrafluoroethylene (PTFE) 13 mm filter 0.45 μm pore size were purchased from Fisher Scientific (UK).

2.2.2. Instrumentation

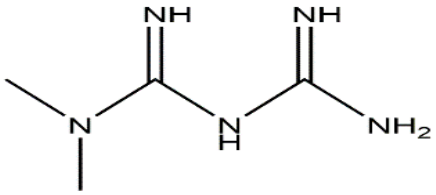
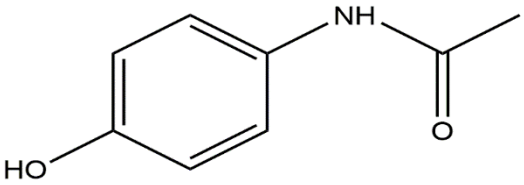
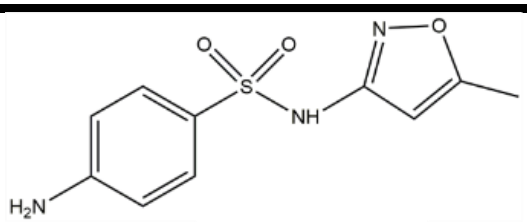
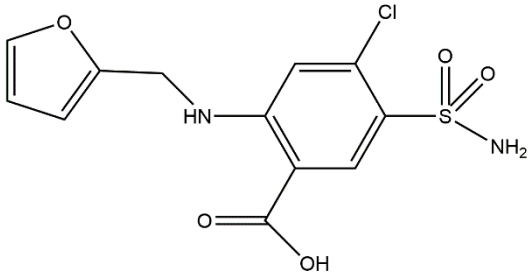
Fisherbrand waterbath (Fisher Scientific, UK), Sartorius BP 210 D balance (Sartorius Ltd UK), Buchi R114 Rotavapor (Buchi, Switzerland), SevenCompact S210 pH meter (Mettler Toledo, Switzerland), Vortex-Genie 2 vortex mixer (Scientific Industries Inc, USA), D8 Advance AXS Bruker Powder diffractometer (Bruker Inc., USA), Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A), autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector (G1329A), Chemstation software (Agilent Technologies, USA)), Chrompack CP-9003 series GC system coupled with a Varian 4400 integrator (Varian Instruments, USA).

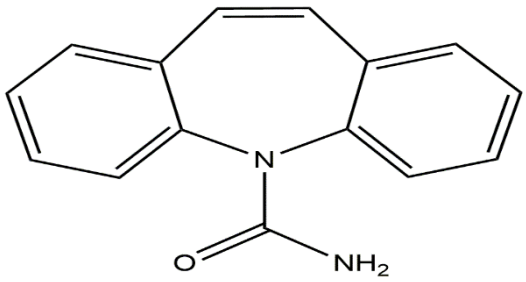
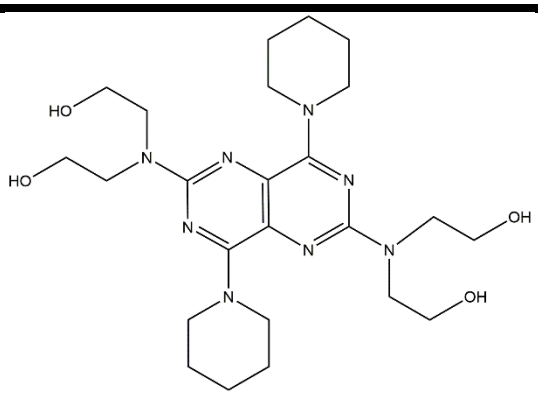
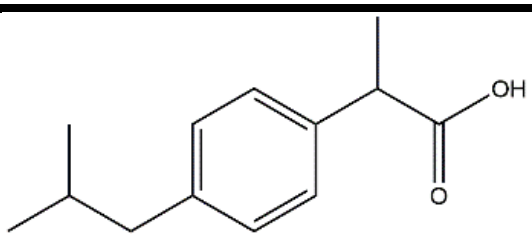
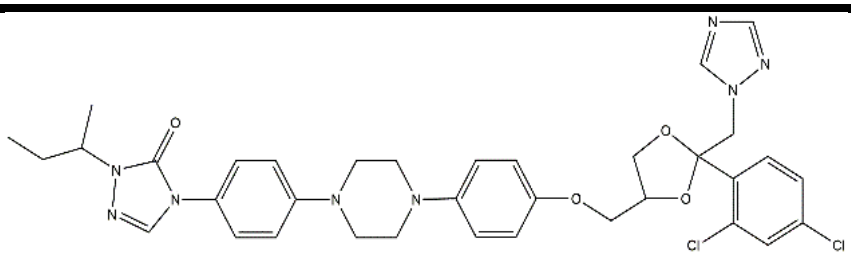
2.2.3. Methods

2.2.3.1. Compounds selected for solubility experiments

The compounds used for the solubility experiments, their physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and their structure are presented in **Table 2.1**.

Table 2.1: Physicochemical properties and structure of the compounds used for the solubility experiments. (ChemDraw Professional 15)

Drug	Ionization	Lipophilicity (log P)*	Solubility
			
Metformin (MTF)	Weak base (pKa=2.8) [20]	-0.5[a]	High [20]
			
Paracetamol (PRC)	Neutral (pKa=9.38) [21]	0.46[a]	High [21]
			
Sulfamethoxazole (SMX)	Weak acid (pKa_1=1.7, pKa_2=5.6) [22]	0.89[a]	Low [23]
			
Furosemide (FRS)	Weak acid (pKa=3.8) [24]	2.29 [24]	Low [24]

			
Carbamazepine (CBZ)	Neutral (pKa=15)[a]	2.45[a]	Low[a]
			
Dipyridamole (DPL)	Weak base (pKa=6.2) [25]	2.74 [26]	Low [27]
			
Ibuprofen (IBU)	Weak acid (pKa=4.5) [28]	3.97[a]	Low [28]
			
Itraconazole (ITZ)	Weak base (pKa=4.5) [29]	5.66[a]	Low [30]

*Experimental values

[a]Source: DrugBank

2.2.3.2 Media prepared for solubility experiments

Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to the method described in the United States Pharmacopeia [31]. Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF-V2) were prepared as per literature references [32].

2.2.3.3. Design of Experiments (DoE) used for solubility studies

A full-factorial Design of Experiments (DoE) was performed to determine the number of necessary experiments using StatGraphics Centurion XVII (Statpoint Technologies Inc, USA). As drug solubility will differ according to the composition of the studied media (pH, presence of bile salts), two models for the DoE were constructed to discriminate between the effects of excipients on drug solubility in compendial (Model 1) and biorelevant conditions (Model 2). The investigated factors were: i. compound (**Table 2.1**), ii. excipient brand (MgSt-BDH, Ligamed MF-2-V, Ligamed MF-3-V), iii. excipient level (low, high), iv. medium (gastric, intestinal). The impact of each excipient on drug apparent solubility [expressed as the relative increase or decrease in presence compared to absence of excipient (Section 2.2.3.6)] was set as the response. A total of 96x3 experiments was determined for each model. 16x3 additional experiments for each model were conducted to determine drug apparent solubility in the corresponding media in the absence of excipient. These experiments were not included in the DoE as drug solubility in excipient absence was measured only for the calculation of relative excipient effects on drug solubility.

2.2.3.4. Characterization of MgSt

2.2.3.4.1. Determination of Relative Content of Stearic and Palmitic Acid

The relative content and total sum of stearic and palmitic acid for each MgSt brand were determined after esterification of the fatty acids with methanol/boron trifluoride followed by gas chromatography according to the proposed method in the USP monograph of MgSt [33].

2.2.3.4.2. Powder X-Ray Diffraction

X-ray powder diffraction (XRPD) measurements for each MgSt brand were obtained. Samples were mounted on an acrylic wafer and analysed at $\lambda = 1.5418$ Å. Samples were measured in reflection geometry in the $\theta - 2\theta$ configuration over the

scan range 2°θ to 40°θ with a 0.12 second exposure per 0.02° increment. The X-rays were generated by a Cu long-fine focus tube operated at 40kV and 40mA. Excipient CRS was determined by the intensity of diffractograms (counts) at the 5° 2θ scale.

2.2.3.4.3. Particle Size Distribution and Specific Surface Area

The PSD of the MgSt brands was measured using laser diffraction in dry dispersion mode at a dispersion pressure of 0.5 bar. The cumulative undersized particle parameters d_{10} (μm), d_{50} (μm) and d_{90} (μm) were calculated. Morphological evaluation of the studied MgSt brands was conducted using Scanning Electron Microscopy (SEM). The SSA of the studied MgSt brands was determined using the Brunauer-Emmett-Teller (BET) method using the nitrogen adsorption method in a relative pressure range of 0.05 – 0.30 Pa [34].

2.2.3.5. Solubility studies

Drug solubility studies in absence and presence of excipient were performed in triplicate using the shake-flask method [35]. Drug excess and 2% w/w or 5% w/w of each excipient were weighed and placed in centrifuge tubes. The amount of excipient was determined as follows: i. for poorly soluble drugs, considering an average of 500 mg tablet weight [36] (which resulted in 9% w/w (low level) and 20% w/w (high level) of excipient in the total volume of the physical mixture) and ii. for highly soluble drugs, according to the amount of drug excess and the relative ratio of drug-excipient based on point (i). The physical mixtures were vortexed for 3 minutes. 5 mL of each medium were added in the tubes and the samples were placed in a shaking water bath (37 °C, 200 strokes per minute (spm)). At 0.5, 4 and 24 hours (for PRC, SMX, CBZ, DPL, IBU) and at 24 hours (for MTF, FRS, ITZ), 500 μL were sampled and filtered through PTFE filters (or cellulose nitrate filters for the cases of IBU and CBZ). Filter adsorption studies were prior performed in triplicate for each drug. No adsorption issues onto the filters used were observed for the studied drugs. Filtered samples were further diluted (if needed) with the corresponding medium and analysed by HPLC (**Table 2.2**). Analytical HPLC procedures for drug quantification in the samples were modifications of already published methods. Drug quantification was made based on calibration curves. Standards were prepared from concentrated stock solutions consisting of drug dissolved in MeOH. As changes in the pH of solutions by presence of dissolved drug [27] or MgSt [37, 38] may affect drug solubility, the pH of samples

after the completion of each experiment was measured. Drug apparent solubility was calculated based on the sample drug concentration measured. Solubility values in excipient absence measured experimentally for neutral drugs, for weak acids in acidic media and for weak bases in basic media determined the intrinsic solubility values. Solubility values in absence of excipient measured experimentally in basic media (for weak acids) and acidic media (for weak bases) determined drug solubility of the ionized molecules

Table 2.2: HPLC methods used for drug quantification

	Column	Mobile Phase	Flow Rate (mL/min)	Temp (°C)	Inj. Vol. (µL)	Detection wavelength (nm)	R_t (min)	Concentration of stock solutions (mg/mL)	Calibration range in acidic media (µg/mL)	Calibration range in basic media (µg/mL)	Reference
MTF	Inertsil Phenyl C18 (Metachem) 250x3mm - 5µm	MeOH/Phosphate buffer pH 7 (70:30)	1	20	20	236	8	2	10 - 200	10 - 200	[39]
PRC	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (20:80)	1	20	20	257	6	2	10 - 200	10 - 200	[40]
SMX	Polaris (Metachem) C18 250x4.6mm – 5µm	MeOH/Phosphate buffer pH 6.8 (20:80)	1	25	20	257	7	1	10 - 200	50 – 500	[41]
FRS	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/water with 0.1% formic acid (50:50)	1	25	50	232	4	1	2 – 20	10 - 200	[42]
CBZ	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (60:40)	1	25	100	285	4	1	10 – 150	10 - 150	[43]
DPL	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/water with 0.1% TFA (30:70)	1	25	50	284	6	1	10 -200	Compendial 1 - 5 Biorelevant 2 - 10	[44]
IBU	Eclipse XDB-C18(Agilent) 250x4.6mm – 5µm	MeOH/water with 0.2% acetic acid (65:35)	1	25	100	233	6	1	5 – 40	10 - 200	[45]
ITZ*	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/phosphate buffer pH 3 (60:40)	1	20	100	Emission: 252 Excitation: 360	8	0.1	Compendial 0.5 – 5 Biorelevant 0.1 - 10	0.015 – 0.06	[46]

*Quantification was made using HPLC-Fluorescence

2.2.3.6. Treatment of *in vitro* solubility data

The Relative Effect (RE) of each excipient on drug apparent solubility was calculated based on equation 2.1:

$$RE = \frac{(S-Sr)}{Sr}\ x\ 100 \qquad \text{(Equation 2.1)}$$

where S and Sr denote drug apparent solubility in presence and absence (reference solubility) of excipient at 0.5, 4 and 24 hours. REs of excipients on drug apparent solubility > 25% or < -20% were considered as significant changes in drug apparent solubility to assess excipient criticality (this range was selected as a similar range is set in order to assess differences in drug exposure after oral administration; i.e. in bioequivalence studies) [47].

Box plots depicting the impact of excipients on drug solubility at 24 hours for all the studied compounds in presence of all the studied MgSt brands or as a function of time (0.5, 4 and 24 hours) for PRC, CBZ, SMX, IBU, DPL in presence of MgSt-BDH and Ligamed MF-2-V were constructed using Spotfire 7.10.1 (TIBCO software Inc, USA). The classification gradient maps portraying the impact of excipients on drug apparent solubility as a function of drug aqueous solubility were generated using SigmaPlot 13.0 (Systat Software Inc, USA). For the construction of 3D mesh plots depicting the impact of excipients (Ligamed MF-2-V, Ligamed MF-3-V) on drug apparent solubility as a function of drug ionization and drug lipophilicity, the REs on drug apparent solubility were smoothed via the Locally Weighed Scatterplot Smoothing (LOWESS) regression to allow better visualization using SigmaPlot 13.0 (Systat Software Inc, USA).

In cases where drug intrinsic solubility was not determined experimentally, the theoretical intrinsic solubility was calculated using the solubility-pH equations (Equations 3.2-3.5) [48]:

$$\log S = \log S_o + \log(10^{-pKa+pH} + 1) \qquad \text{for weak acids (Equation 2.2)}$$

$$\log S = \log S_o + \log(10^{pKa-pH} + 1) \qquad \text{for weak bases (Equation 2.3)}$$

$$\log S = \log S_o + \log(10^{+pKa_2+\ pKa_1-2pH} + 10^{pKa_2-pH} + 1) \qquad \text{for diprotic bases (Equation 2.4)}$$

$\log S = \log S_o + \log(10^{+\,pKa_1 - pH} + 10^{-pKa_2 + pH} + 1)$ for ampholytes (Equation 2.5)

where S and S_o indicate drug solubility at the given pH and the intrinsic solubility, respectively. The final pH and experimental solubility values of the ionized drug in basic (for weak acids) or acidic media (for weak bases) were used for the calculation of the theoretical intrinsic solubility. Theoretical pH-solubility profiles in the physiological pH range were constructed to assess if changes in the pH of the medium could justify differences in drug solubility by excipient presence. The final pH and intrinsic solubility values (experimental or theoretical) were used for the construction of the theoretical pH – solubility profiles in the physiological pH range based on Equations 2.2-2.5.

2.2.3.7. Multivariate Analysis of *in vitro* solubility data

Excipient REs on drug apparent solubility were correlated to drug physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility), excipient critical material attributes (CRS, PSD, level) and medium characteristics (gastric, intestinal) by partial least squares (PLS) regression using the XLSTAT software (Microsoft, USA). Two models for the REs of excipients on drug apparent solubility in compendial media (Model 1) and biorelevant media (Model 2) were constructed. The evaluated variables for both models were categorized according to their type as categorical (expressing a category or type) and numerical (measurements with numerical meaning). Categorical variables included: i. drug solubility (poor, high), ii. excipient level (low, high), iii. medium (gastric, intestinal) while numerical parameters included i. % of drug ionized (F_{ion}; calculated based on the Henderson – Hasselbalch equation at the pH of each medium), ii. drug lipophilicity (log P), iii. excipient CRS, iv. excipient PSD. Excipient REs on drug solubility at 24 hours were used as the response. The selected interaction terms included each excipient property combined with each drug physicochemical property (drug ionization, drug lipophilicity, drug aqueous solubility) and medium characteristics (gastric, intestinal). Observation diagnostics were performed prior to model analysis to identify outliers in the data set. The distance of each observation to the model in the Y-plane (DmodY) tool based on PLS residuals was used. Plots of standardized DmodY vs each observation were generated and any observation exceeding the

maximum tolerance volume in Y ($D_{crit(Y)}$) was considered an outlier [49, 50]. Exclusion of outliers was based on: i. deviating cases (positive REs) in solubility caused by a shift in the pH of the solution, ii. observations resulting in high variability (coefficient of variation (CV%) > 20%) within the triplicate samples (one value from the triplicate could be excluded as the outlier analysis could detect these values). PLS models generated with and without outlier exclusion (data not shown) confirmed that outlier exclusion did not alter the interpretation of results but only enhanced the predictive ability of the regression model. The generated models were assessed in terms of goodness of fit (R^2) and goodness of prediction (Q^2). High values of R^2 and Q^2 with a difference not greater than 0.2 - 0.3 were indications of successful models [51]. The number of PLS components (lines on the X-space which best approximate and correlate with the Y-vector) was based on minimum predictive residual sum of squares (PRESS) [51]. From the available components the one at which Q^2 reached its maximum value was selected [49]. Standardized coefficients were used to show the direction (positive or negative) and extent of each variable on the response. The significance of the variables was assessed by the variable influence on projection (VIP) value. VIP values > 0.8 were considered as moderately influential in the model while VIP values > 1 were considered the most influential in the model [51]. A 95 % confidence interval was used.

2.2.3.8. Roadmap Design

A roadmap design for the identification of potential risks of MgSt variability on drug apparent solubility was constructed combining the impact of excipients on drug solubility at 24 hours from the solubility studies to excipient (CRS, PSD) and drug (drug ionization, drug lipophilicity, drug aqueous solubility) characteristics. Drugs were categorized according to drug aqueous solubility and drug lipophilicity (**Table 2.1**) and drug ionization (low ionized: $F_{(ion)}$ < 50%, highly ionized: $F_{(ion)}$ > 50%). The risk assessment of the impact of excipients on drug apparent solubility was evaluated by setting reference range criteria of -20% - 25% [47] on the REs of excipients on drug solubility at 24 hours. REs of excipients on drug solubility outside these values (REs < -20% or REs > 25%) were considered critical for oral drug performance.

2.3. Results and Discussion

2.3.1. Characterization of MgSt

2.3.1.1. Determination of Relative Content of Stearic and Palmitic Acid

The relative content and total sum of stearic and palmitic acid for each MgSt brand are presented in **Figure 2.2a**. The relative content varied between 70%:30% of stearic:palmitic acid for MgSt-BDH and Ligamed MF-3-V and 65%:35% of stearic:palmitic acid for Ligamed MF-2-V. The total sum of the fatty acids of the studied brands was > 99%, within the acceptance criteria of the USP monograph of MgSt [33]. As changes in the lubrication efficiency of MgSt have been reported only for differences between the stearic and palmitic relative contents higher than 20% [16], no impact on drug solubility is anticipated by the small differences in the relative fatty acid content of the studied brands.

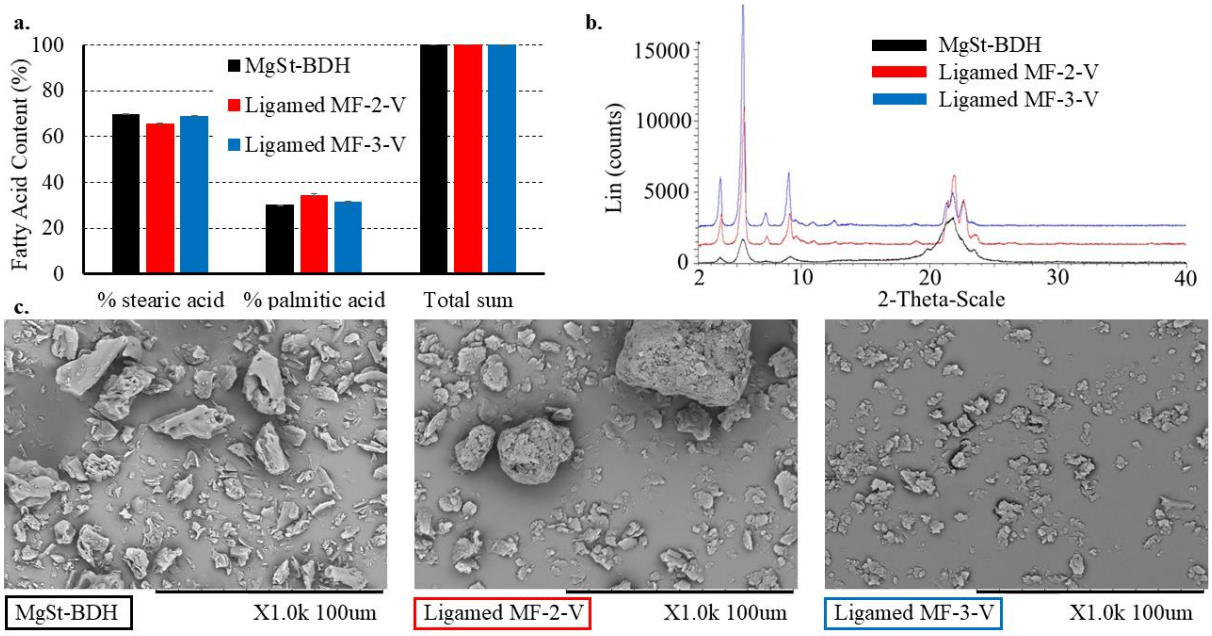


Figure 2.2: a. Relative content (%) and total sum (%) of stearic and palmitic acid, b. XRPD patterns and c. SEM micrographs of the studied brands of MgSt. The different brands are shown as: for i. MgSt - BDH (black colour), ii. Ligamed MF-2-V (red colour) and iii. Ligamed MF-3-V (blue colour).

2.3.1.2. Powder X-Ray Diffraction

The XRPD patterns of MgSt - BDH, Ligamed MF-2-V and Ligamed MF-3-V are shown in **Figure 2.2b**. The patterns are in accordance with previously reported diffractograms [15]. The intensity and sharpness of the peaks at the 3.3° 2θ, 5.5° 2θ and 23° 2θ scale revealed higher crystalline portions for Ligamed MF-2-V and Ligamed MF-3-V compared to MgSt-BDH.

2.3.1.3. Particle Size Distribution

The PSD and SSA analysis of the studied MgSt brands are shown in **Table 2.3**. Ligamed MF-3-V comprised of smaller particles compared to MgSt-BDH and Ligamed MF-2-V. SEM micrographs confirmed these findings (**Figure 2.2c**) as large agglomerates were observed for MgSt-BDH and Ligamed MF-2-V. The SSA was higher for Ligamed MF-3-V compared to MgSt-BDH and Ligamed MF-2-V, due to its lower PSD. Differences in crystallinity between MgSt-BDH and Ligamed MF-2-V (expressed by the differences in the intensity and sharpness of diffractogram peaks, **Figure 2.2b**), could justify the lower SSA of MgSt-BDH compared to Ligamed MF-2-V, despite its lower PSD [52].

Table 2.3: Particle size distribution and specific surface area for MgSt-BDH, Ligamed MF-2-V and Ligamed MF-3-V.

Excipient Brand	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Specific Surface Area (m^2/g)
MgSt-BDH	1.37	6.61	21.1	4.38 (±0.05)
Ligamed MF-2-V	2.13	8.88	36.5	15.85 (±0.73)
Ligamed MF-3-V	1.87	6.92	15.2	20.51 (±0.31)

2.3.2. Solubility studies

2.3.2.1. Impact of the studied MgSt brands on drug apparent solubility

The reference drug solubility values at 24 hours in compendial and biorelevant media are summarized in **Table 2.4**. The reference solubility of neutral drugs (PRC, CBZ) was not pH-depended, as expected. Higher solubility values were observed in biorelevant compared to compendial media for neutral drugs, as the presence of bile

salts improves drug solubilization [53]. Weak acids (SMX, FRS, IBU) and weak bases (DPL, ITZ) showed a pH-dependent solubility in the physiological pH range due to their ionization pattern. The solubility of MTF (weak base) was not pH-depended, as drug was fully ionized in the studied conditions [20]. Due the presence of two pKa constants (**Table 2.1**), SMX is ionized in acidic (80% and 50% of drug ionized in 0.1 N HCl pH 1 and FaSSGF pH = 1.6, respectively) and basic media (92% and 86% in phosphate buffer pH 6.8 and FaSSIF-V2 pH = 6.5, respectively). The reference solubility values of SMX in acidic media were lower compared to their corresponding basic media due to the higher % of ionized drug in basic compared to acidic conditions. In media where weak acids or weak bases were unionized, drug solubility at 24 hours was higher in biorelevant compared to compendial media due to the presence of solubilizing components [53]. In media where weak acids and weak bases (except from the case of MTF) are ionized, drug solubility values were higher in the compendial compared to the biorelevant conditions, despite the absence of solubilizing components. These changes in drug solubility at 24 hours can be explained by the differences in the pH between the studied sets of media which result in higher % of drug ionized in compendial compared to biorelevant conditions and therefore higher reference drug solubility [54].

Table 2.4: Reference solubility values (μg/mL) at 24 hours of the studied drugs in compendial and biorelevant media. (Mean ± SD, n = 3)

	Compendial Media		**Biorelevant Media**	
Drug	**0.1 N HCl pH 1**	**Phosphate buffer pH 6.8**	**FaSSGF**	**FaSSIF-V2**
MTF	3.1×10^5 ($\pm0.3\times10^5$)	3.1×10^5 ($\pm0.2\times10^5$)	3.4×10^5 ($\pm0.8\times10^5$)	4.3×10^5 ($\pm0.4\times10^5$)
PRC	1.6×10^4 ($\pm 0.1\times10^4$)	1.5×10^4 ($\pm 0.1\times10^4$)	1.7×10^4 ($\pm 0.2\times10^4$)	1.7×10^4 ($\pm 0.1\times10^4$)
SMX	1.6×10^3 ($\pm 0.1\times10^3$)	3.7×10^3 ($\pm 0.1\times10^3$)	862 (±21)	1.3×10^3 ($\pm 0.1\times10^3$)
FRS	14 (±2)	3.4×10^3 ($\pm1.4\times10^2$)	15 (±1)	1.6×10^3 ($\pm3.0\times10^2$)
CBZ	265 (±6)	227 (±9)	368 (±1)	280 (±7)

DPL	1.3×10^4 ($\pm9.1\times10^2$)	5 (±1)	8.6×10^3 ($\pm2.0\times10^2$)	13 (±1)
IBU	43 (±3)	5.5×10^3 ($\pm 6.7\times10^2$)	44 (± 5)	1.5×10^3 (± 5.8)
ITZ	11 (±1)	-*	1.2 (± 0.2)	0.05 (± 0.01)

*below limit of detection of the analytical method

The effects of the MgSt brands on the solubility of the studied compounds at 24 hours in compendial and biorelevant media are presented in **Figures 2.3** and **2.4**, respectively.

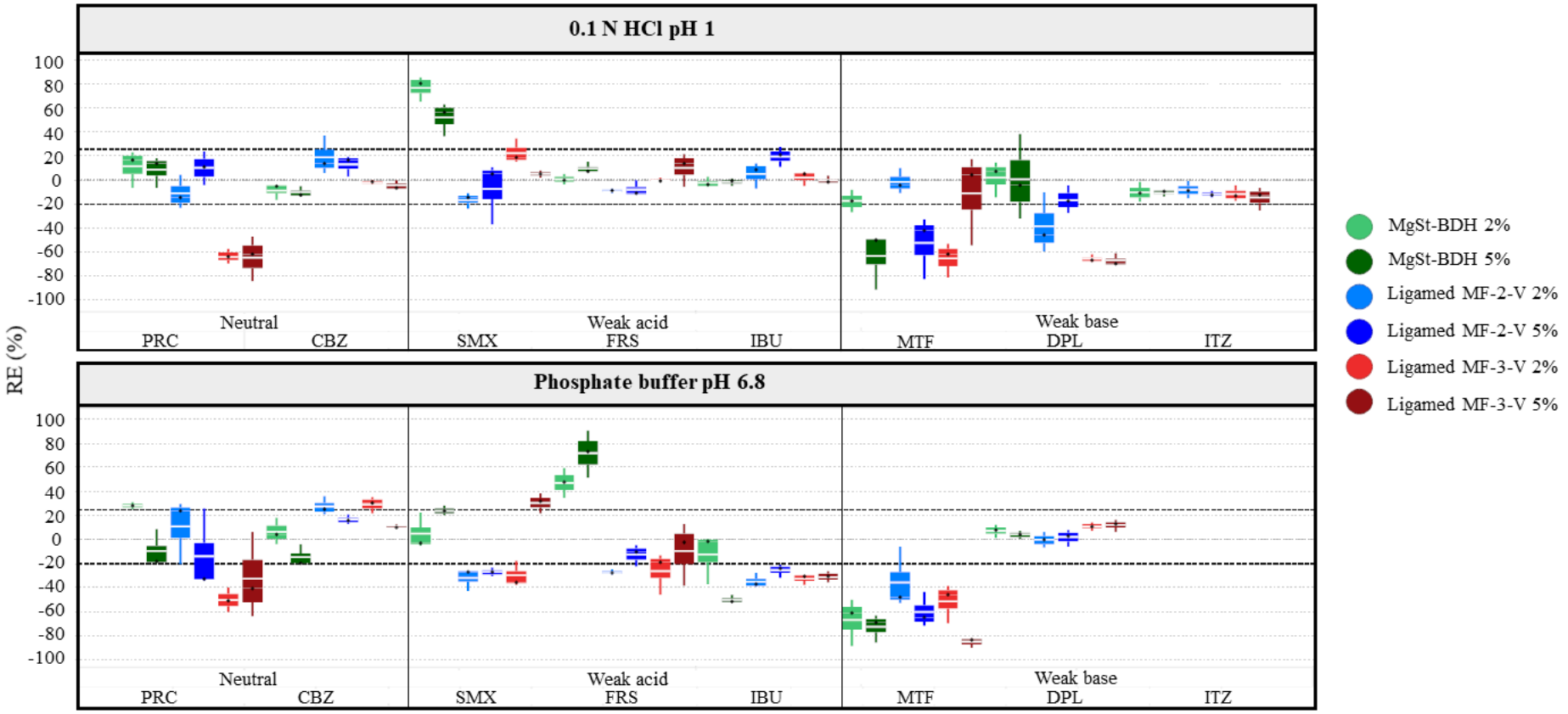


Figure 2.3: Box plots of the relative effects (%) of the MgSt brands on drug solubility at 24 hours in compendial media. The excipient brands are shown as: i. MgSt-BDH (green colour), ii. Ligamed MF-2-V (blue colour) and iii. Ligamed MF-3-V (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

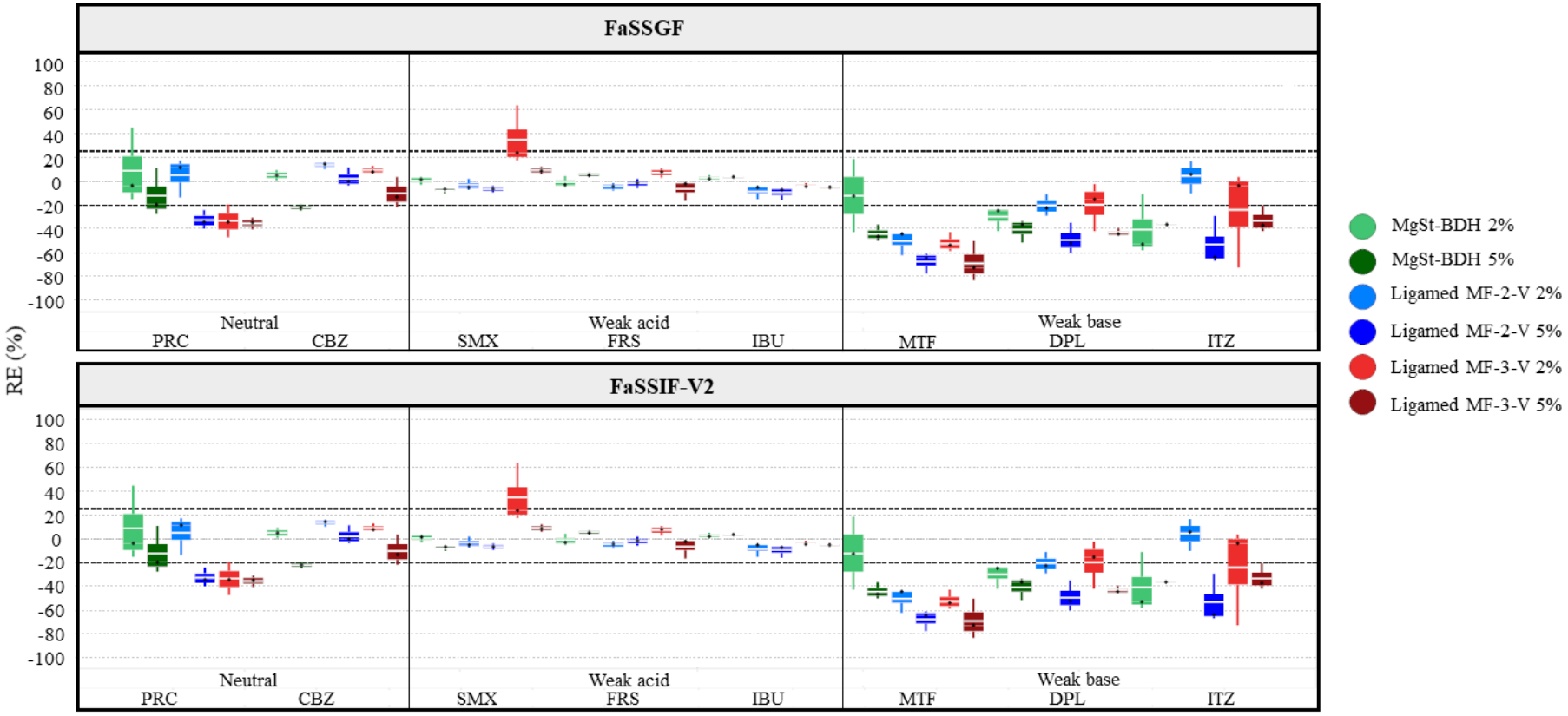


Figure 2.4: Box plots of the relative effects (%) of the MgSt brands on drug solubility at 24 hours in biorelevant media. The excipient brands are shown as: i. MgSt-BDH (green colour), ii. Ligamed MF-2-V (blue colour) and iii. Ligamed MF-3-V (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

Neutral drugs: Cases of significant decrease in drug solubility at 24 hours (-65% < REs < -32%) by the studied MgSt brands were observed for the case of PRC. For PRC, an increase in the pH of the media was observed in presence of MgSt in 0.1 N HCl pH 1 (0.1 – 0.6 pH units) and in biorelevant media (0.3 – 5 pH units) due to the basic nature of the excipient [37, 38], however changes in the pH of the media cannot justify the differences in PRC solubility in MgSt presence at 24 hours (**Figure 2.5**). The reduction in PRC solubility at 24 hours by MgSt can be explained by the decreased drug-medium contact in excipient presence [55]. The hydrophobic nature and slow dissolution of MgSt from the powder surface [7, 8] which further limit drug dissolution and/or drug solubilization could also contribute to the decrease in drug apparent solubility. The effects of MgSt-BDH and Ligamed MF-2-V on drug solubility as a function of time for one highly soluble (PRC) and 4 poorly soluble drugs (CBZ, SMX, IBU, DPL) in compendial and biorelevant media are presented in **Figure 2.6**. Presence of MgSt resulted in pronounced decrease in PRC solubility (–90 % < REs < -60 %) at early time points (0.5 and 4 hours) confirming that the reduction in drug solubility by MgSt presence relates to the lipophilic nature of the excipient. Significant increase in drug solubility at 24 hours was observed in phosphate buffer pH 6.8 for PRC (2% MgSt-BDH: RE = 28%) and for CBZ (2% of Ligamed MF-2-V: RE = 29%, Ligamed MF-3-V: RE = 27%) and in FaSSIF-V2 for PRC (2% of Ligamed MF-2-V: RE = 27%) (**Figures 2.3 and 2.4**). The observed slight differences in the pH of the media (0 – 0.2 pH units) due to the presence of MgSt [37, 38] are not expected to affect the solubility of neutral drugs (**Figure 2.5**). As MgSt particles disperse in basic conditions [19], the observed increase in drug solubility at 24 hours could be attributed to improved drug powder dispersion which facilitates drug solubilization.

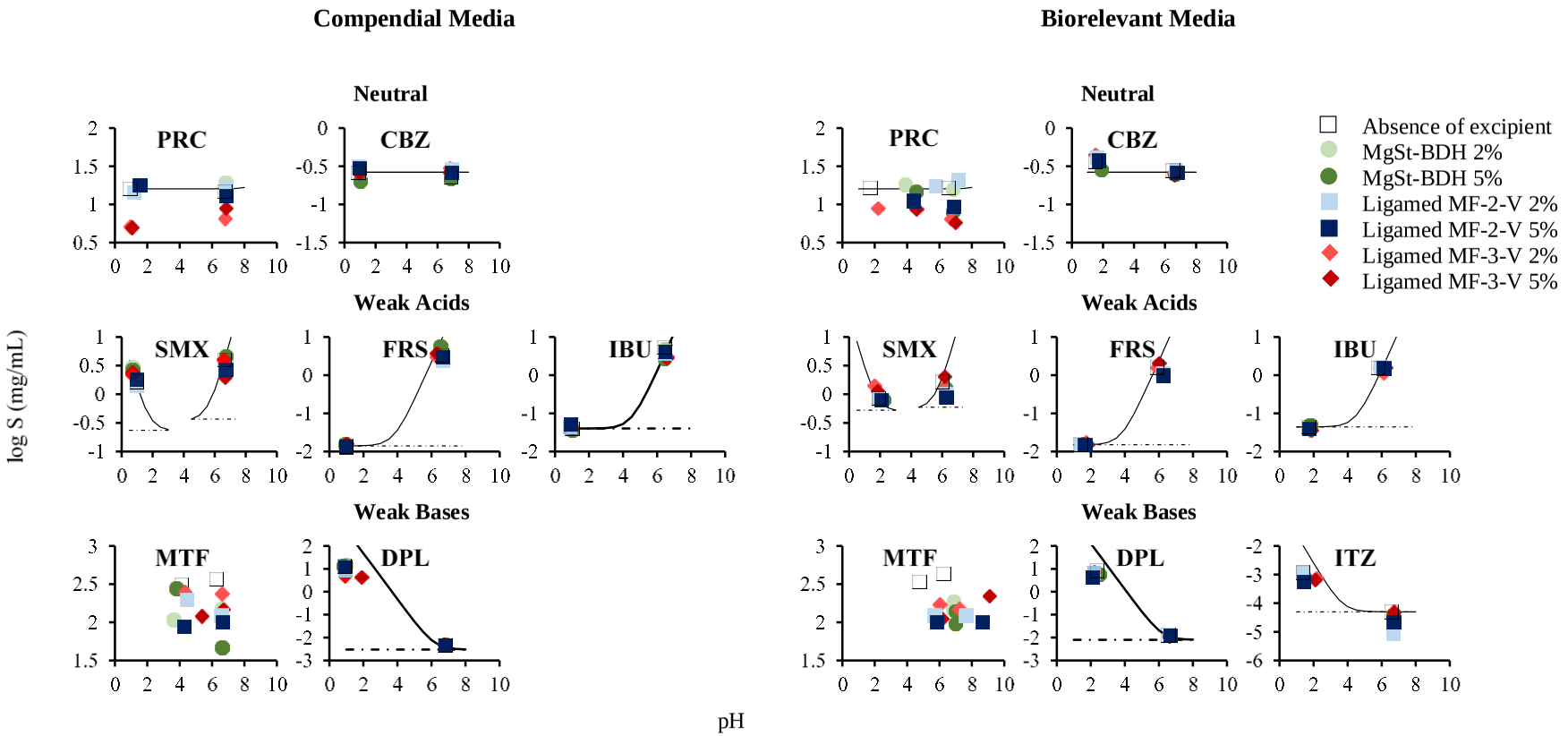


Figure 2.5: Theoretical pH-solubility profiles of the studied drugs in compendial and biorelevant media and experimental solubility values of the studied drugs in absence (squares) and presence of excipients (i. MgSt-BDH (green colour), ii. Ligamed MF-2-V (blue colour), iii. Ligamed MF-3-V (red colour)). Light and dark colours correspond to low and high excipient level. Dashed lines indicate drug intrinsic solubility.

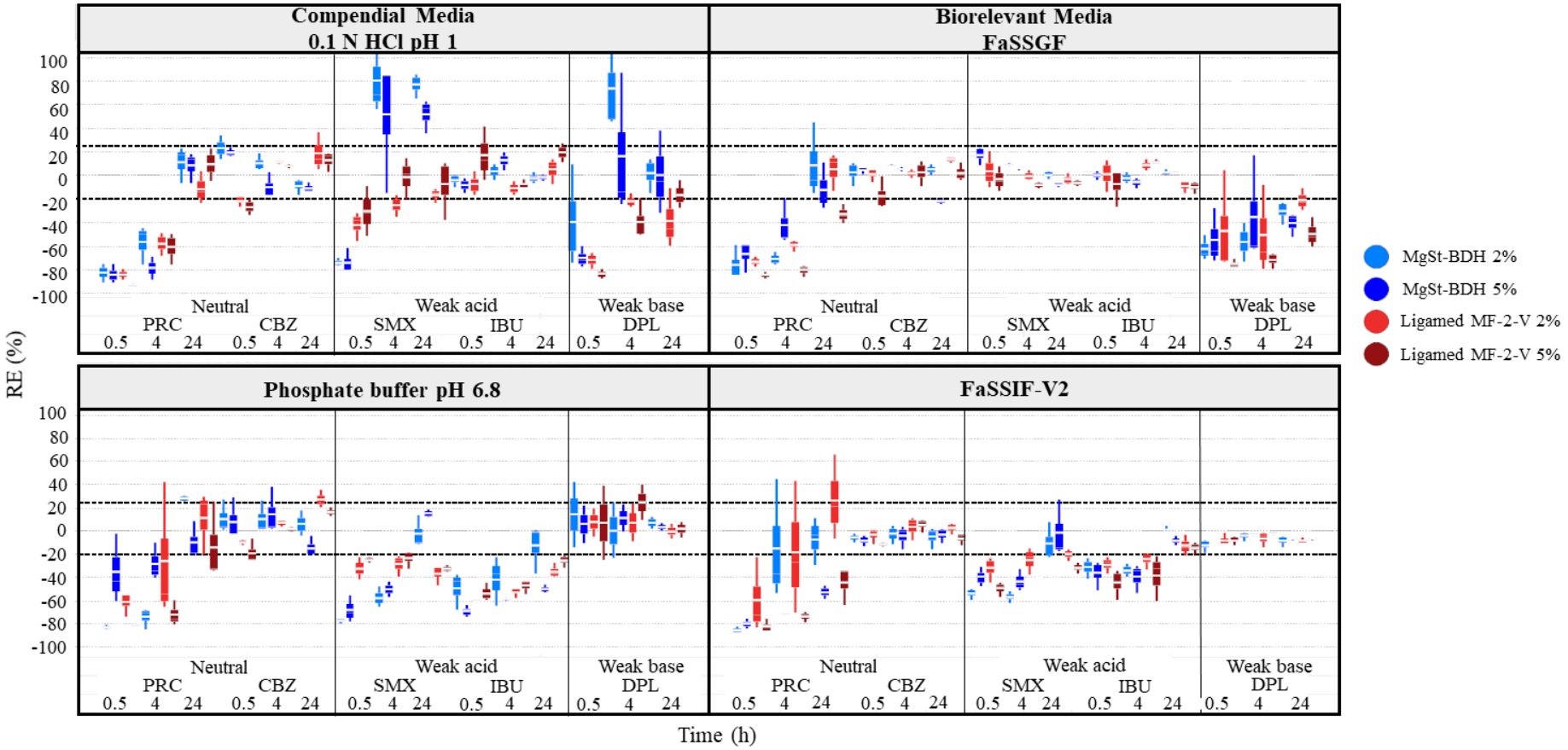


Figure 2.6: Box plots of relative effects (%) on the solubility of PRC, CBZ, SMX, IBU, DPL in compendial and biorelevant media as a function of time (h) in presence of i. MgSt-BDH (blue colour) and ii. Ligamed MF-2-V (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean, n = 3)

Weak acids: Cases of significant reduction in the solubility of weak acids by MgSt presence at 24 hours was observed mainly in basic conditions (SMX: -30% < REs < -20%, FRS: -40% < REs < -25%, IBU: -50% < REs < -25%) (**Figures 2.3 and 2.4**). For cases where MgSt presence significantly decreased drug apparent solubility, small changes in the pH of the acidic media occurred in absence or presence of excipient (± 0.1 pH units) while the pH of the basic media decreased in absence or presence of excipient (0.2 – 0.7 pH units), potentially due to the dissociation of weak acids. The construction of the theoretical pH-solubility profiles (**Figure 2.5**) revealed that in cases where MgSt significantly reduced drug solubility at 24 hours, the changes in the pH of media in excipient presence cannot justify the changes in drug solubility, as the experimental solubility values in excipient presence do not correspond to the theoretical solubility values (expected according to the changes in the pH of the media). The reduced drug dissolution and/or drug solubilization by the lipophilic MgSt [7, 8, 55] can explain the observed reduction in drug apparent solubility by MgSt, as in the case of neutral drugs. The impact of MgSt-BDH and Ligamed MF-2-V on the SMX and IBU solubility through time (**Figure 2.6**) showed that the reduction in drug solubility by MgSt was higher at early (-80% < REs < -20%) compared to late time points (24 hours), even in several cases where MgSt did not significantly alter the 24 hour drug solubility. This observation confirms that the reduction in drug apparent solubility is a result of reduced powder wetting in presence of MgSt. Significant increase in the 24 hour drug solubility in acidic media was observed for SMX in 0.1 N HCl pH 1 (MgSt-BDH: REs of 77% and 52% for the low and high level, respectively) and in FaSSGF (2% Ligamed MF-3-V: RE = 34%) (**Figures 2.3 and 2.4**). In the aforementioned cases, the pH of the medium in presence was lower (0.1 N HCl pH 1: pH = 0.7 in presence of MgSt-BDH, FaSSGF: pH = 1.64 in presence of Ligamed MF-3-V) compared to excipient absence (0.1 N HCl pH 1: pH =0.94, FaSSGF: pH =1.89). The increase in drug solubility at 24 hours is therefore attributed to the change in the pH of the media as experimental and theoretical drug solubilities in excipient presence are identical (**Figure 2.5**) (further investigations of the interplay between drugs/excipients and the pH of the medium are needed as MgSt is not expected to reduce the pH of the medium). Significant increase in drug apparent solubility was also observed in basic conditions for FRS (MgSt-BDH: REs of 47% and 71% for the low and high level, respectively) and SMX in phosphate buffer pH

6.8 (5% Ligamed MF-2-V: RE = 30%) and for FRS in FaSSIF-V2 (5% Ligamed MF-3-V: RE = 28%). For the above cases, the reduction in the pH of the medium was lower in presence (approximately 0.2 - 0.3 pH units) compared to excipient absence (0.2 – 0.6 pH units) potentially due to the basic nature of MgSt [37, 38] and explains the differences in drug solubility at 24 hours between excipient absence and presence (**Figure 2.5**).

Weak bases: Significant reduction in the solubility of weak bases by MgSt presence at 24 hours was observed for the majority of cases (MTF: -84% < REs < -35%, DPL: -67% < REs < -20%, ITZ: -50% < REs < -20%) (**Figures 2.3 and 2.4**). The impact of pH on the solubility of weak bases cannot be evaluated, as the theoretical pH-solubility profiles did not follow the exponential increase in drug solubility with increasing pH due to *in situ* salt formation between the drugs and counterions of the medium [56] (**Figure 2.5**). The hydrophobic nature of MgSt [7, 8, 55] leading to slow drug dissolution and/or drug solubilization could justify the decrease in drug apparent solubility. The impact of excipients (MgSt-BDH, Ligamed MF-2-V) on the solubility of DPL through time (**Figure 2.6**) showed a pronounced reduction in DPL solubility at early time points only in acidic media confirming the negative impact of MgSt on drug dissolution/solubilization (only in presence of 2% BDH an increase was observed in DPL solubility at 4 hours in 0.1 N HCl pH 1). For weak bases, significant increase in drug solubility at 24 hours by MgSt presence was not observed (**Figures 2.3 and 2.4**).

The solubility data showed increased variability in the cases where MgSt presence significantly affected drug solubility at 24 hours (PRC, MTF: CV% > 40%, highly ionized drugs: 20% < CV% < 40%). As working with physical mixtures may yield high standard deviations due to the heterogeneous dispersion of the constituents [57, 58], the increased variability can be attributed to the heterogeneous distribution of excipient particles on the powder surface.

2.3.2.2. Impact of excipients on drug apparent solubility based on drug physicochemical properties

The effects of MgSt on the solubility of neutral drugs, weak acids and weak bases at 24 hours as a function of drug ionization and drug lipophilicity in compendial and biorelevant media are presented in **Figure 2.7**.

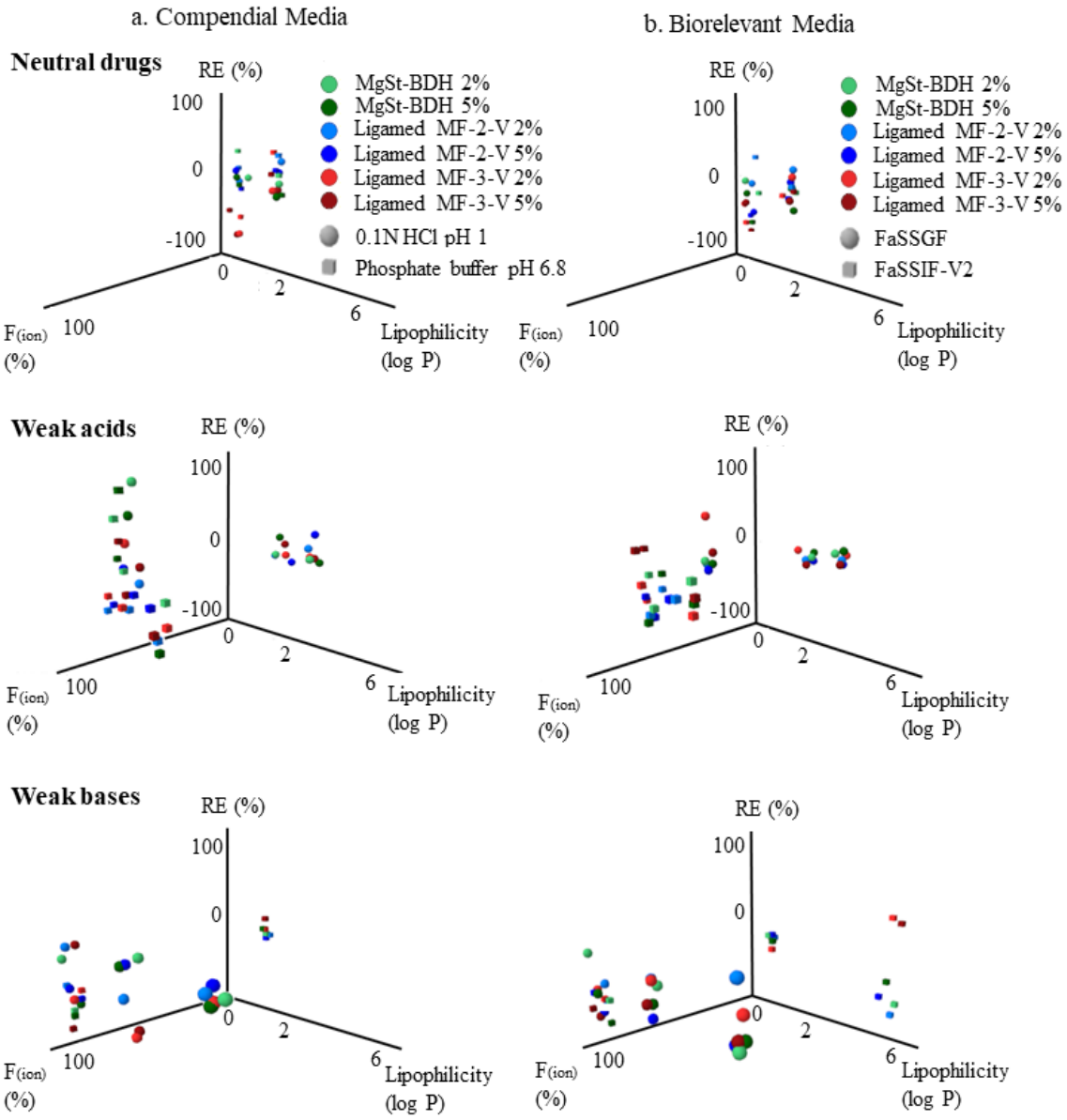


Figure 2.7: Relative effects (%) of MgSt brands on drug solubility at 24 hours as a function of drug ionization (%) and drug lipophilicity (log P) in a. compendial and b. biorelevant media. The excipients brands are shown as: i. MgSt-BDH (green colour), ii. Ligamed MF-2-V (blue colour), iii. Ligamed MF-3-V (red colour). Light and dark colours correspond to low and high excipient levels, respectively. Media representing gastric and intestinal conditions are presented as: i. acidic media (circles) and ii. basic media (squares)

As both neutral drugs are unionized under the studied media, the higher decrease in the apparent solubility of PRC compared to CBZ by MgSt is likely attributed to the differences in the lipophilicity of these two compounds (**Table 2.1**). For weak acids

and weak bases, the decrease in drug solubility at 24 hours is pronounced in media where drugs are highly ionized (excluding the cases of increased drug solubility at 24 hours attributed to the change of the pH of the medium). A clear trend between the impact of excipients on the apparent solubility of weak acids and bases and drug lipophilicity cannot be observed. The decrease in drug solubility at 24 hours by MgSt presence was more pronounced with increasing level of drug ionization and/or decreasing drug lipophilicity (**Figure 2.7)**. As in these cases a higher number of drug molecules can dissolve fast in the surrounding medium, powder surface can saturate with the lipophilic MgSt particles leading to decreased drug solubility [19]. The classification gradient map (**Figure 2.8**) depicting the effects of the MgSt brands on drug solubility at 24 hours as a function of decreasing drug aqueous solubility in compendial and biorelevant media confirms this finding. Presence of MgSt decreased the apparent solubility of drugs with high aqueous solubility. For the majority of drugs with low aqueous solubility, drug solubility at 24 hours was not affected by excipient presence, except from the cases of highly ionized drugs.

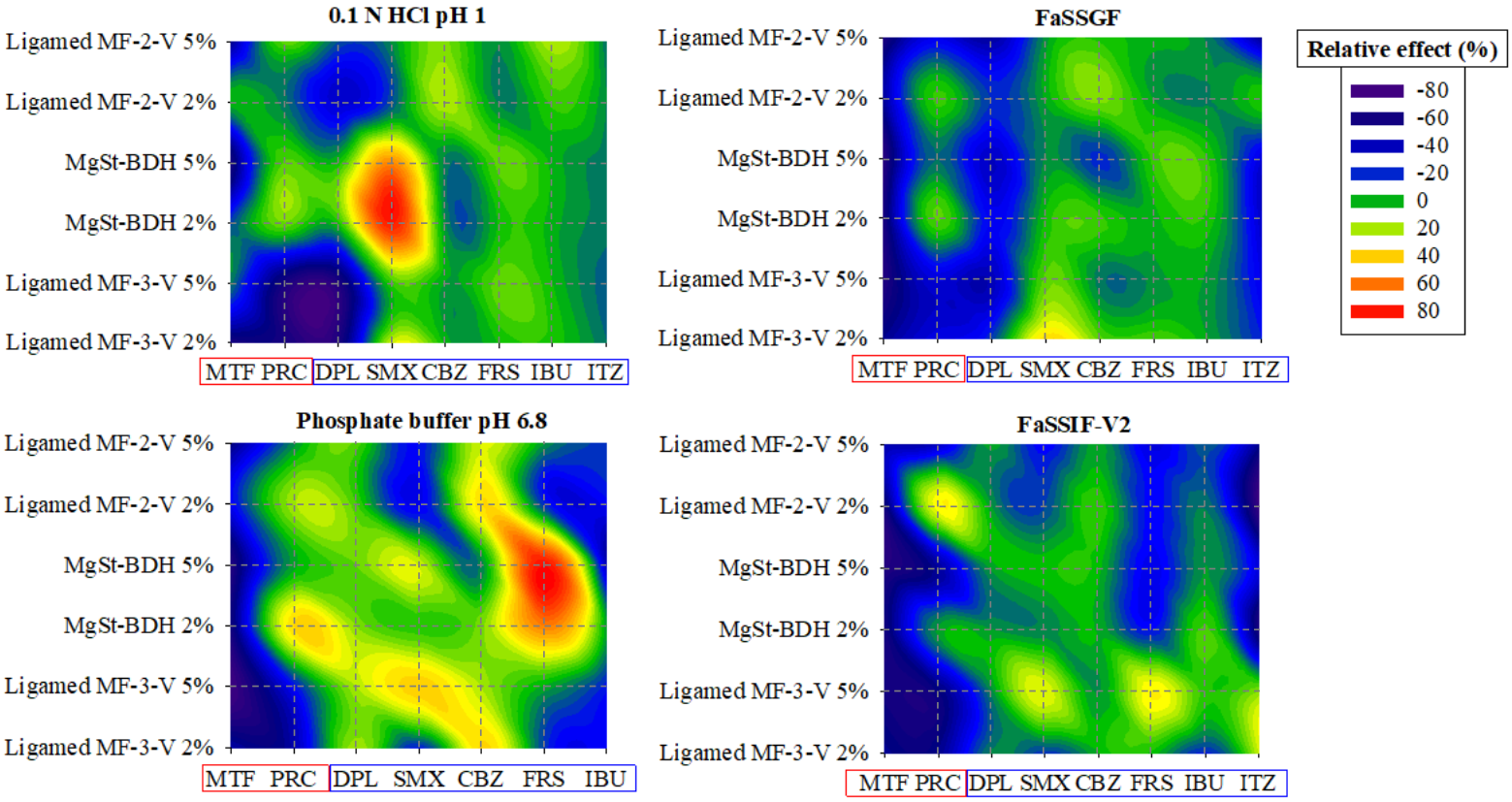


Figure 2.8: Classification gradient maps of the relative excipient effects of the MgSt brands on the solubility of highly and poorly soluble compounds at 24 hours. Y-axes are set in an increasing excipient particle size and excipient level order. The x-axes are set in a decreasing drug aqueous solubility order (red colours for highly soluble and blue colours for poorly soluble drugs).

2.3.2.3. Impact of excipients on drug apparent solubility based on excipient properties

2.3.2.3.1. Impact of MgSt crystallinity on drug apparent solubility

The effects of the studied MgSt brands on drug apparent solubility depended on excipient properties. For the majority of cases, significant reduction in drug solubility at 24 hours was observed mainly in presence of high crystalline brands (Ligamed MF-2-V, Ligamed MF-3-V) compared to the low crystalline brand (MgSt-BDH) (**Figures 2.3 and 2.4**). In cases where all the studied brands decreased drug solubility at 24 hours, the reduction in drug solubility was more pronounced by the high crystalline (-85% < REs < -20%) compared to the low crystalline brand (-70% < REs < -20%). Investigation of the impact of the low (MgSt-BDH) and a high crystalline (Ligamed MF-2-V) brand on drug solubility through time (**Figure 2.6**) showed that the crystalline brand resulted in the same or higher reduction in drug solubility at early time points (0.5 and 4 hours) compared to the less crystalline brand (except from the case of SMX in 0.1 N HCl pH 1 and phosphate buffer pH 6.8). The better lubrication efficiency of crystalline brands around particles during mixing could explain the more pronounced delay on drug dissolution [18].

2.3.2.3.2. Impact of MgSt PSD and level on drug apparent solubility

As the impact of PSD on the lubrication efficiency of MgSt will have greater magnitude for crystalline brands [18], the impact of increasing MgSt particle size on drug solubility at 24 hours was investigated for the two crystalline MgSt brands (Ligamed MF-2-V and Ligamed MF-3-V). The effects of Ligamed MF-2-V and Ligamed MF-3-V on drug solubility at 24 hours as a function of drug ionization and drug lipophilicity are presented in **Figure 2.9**.

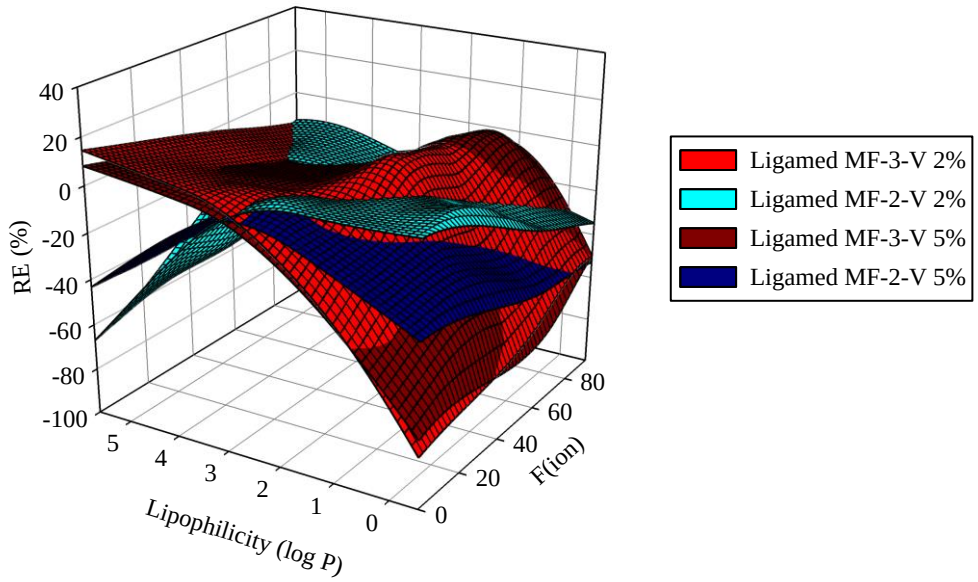


Figure 2.9: Relative effects (%) of i. Ligamed MF-2-V (blue colour) and ii. Ligamed MF-3-V (red colour) on drug solubility at 24 hours as a function of drug ionization (%) and lipophilicity (log P). Light and dark colours correspond to low and high excipient level, respectively.

Differences in the REs of excipients on drug apparent solubility within the two brands are observed in the low drug ionization range. Presence of the low particle size brand (Ligamed MF-3-V) reduced the solubility of drugs with log P < 1 in a higher extent (REs < -60%) compared to the high particle size brand (Ligamed MF-2-V) (REs < -40%) at 24 hours. The higher reduction in drug apparent solubility in presence of Ligamed MF-3-V compared to Ligamed MF-2-V can be explained by the creation of a stronger and uniform coating around drug particles by MgSt of low particle size [11]. The opposite is observed when increasing drug lipophilicity (log P > 4, ITZ). Based on our complete data set, presence of MgSt should not affect the solubility of poorly soluble unionized drugs at 24 hours (**Figure 2.7**), therefore further investigations are needed to explain why low particle size brands affected the solubility of ITZ in media where the drug was unionized. Increasing excipient level resulted in pronounced reduction in drug solubility at 24 hours (REs of approximately -10% and -40% for the low and high excipient level, respectively) only for Ligamed MF-2-V. As high particle size brands (Ligamed MF-2-V) are not able to form a strong layer around particles

compared to low particle size brands (Ligamed MF-3-V), increasing their amount could lead to significant higher drug particle coverage [59].

2.3.3. Multivariate Data Analysis of solubility data

The standardized coefficients of the studied variables and their interactions in compendial and biorelevant media are presented in **Figure 2.10**. The two models showed an average predictive power and fit (compendial media: $Q^2 = 0.5$ and $R^2 = 0.6$, biorelevant media: $Q^2 = 0.4$ and $R^2 = 0.5$).

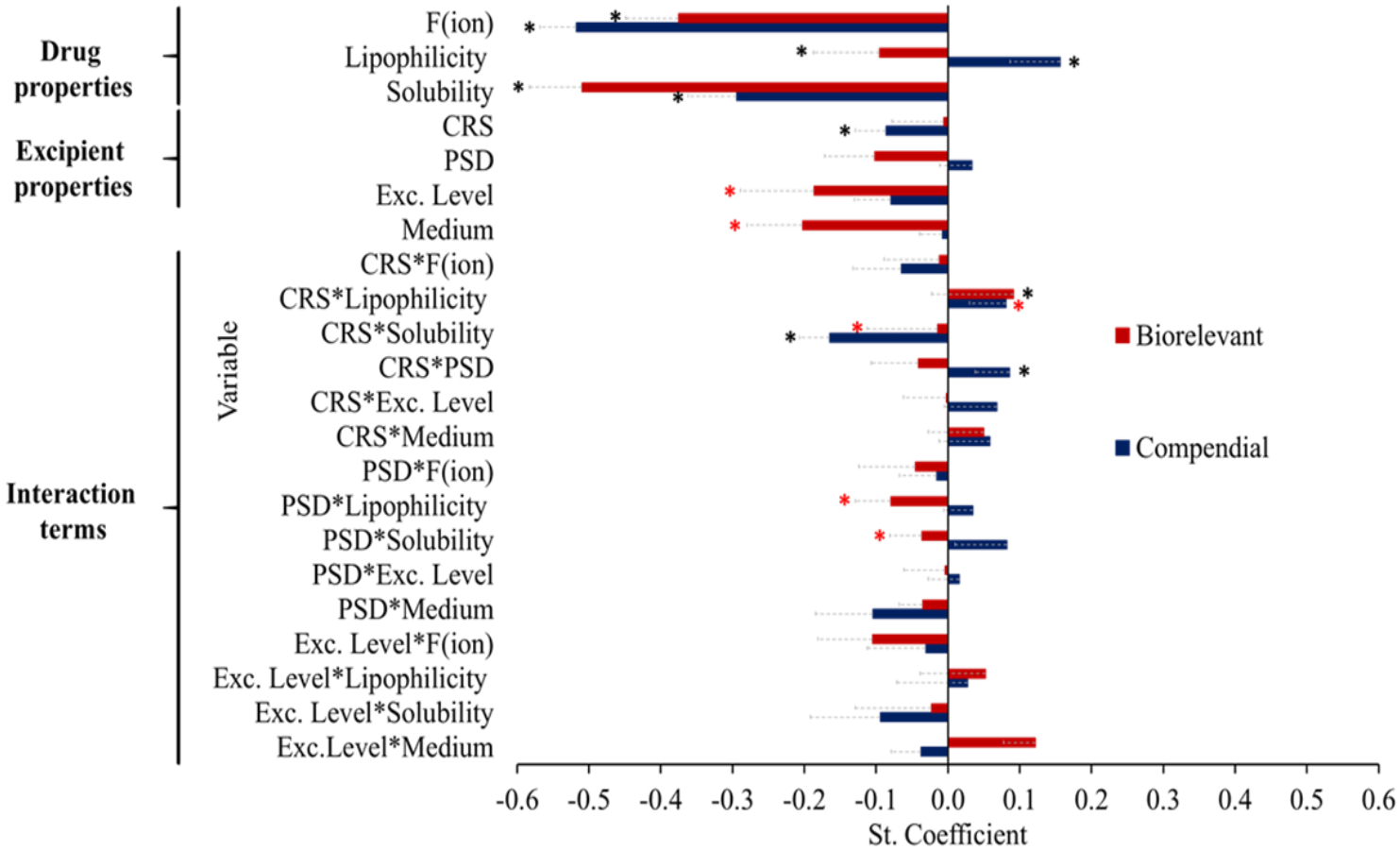


Figure 2.10: Standardized coefficients of the studied variables (and interactions) in compendial (blue colour) and biorelevant (red colour) media. * denotes coefficients of VIP > 1, * denotes coefficients of 0.8 < VIP < 1 (Mean, -SE).

The statistical analysis reveals that the impact of MgSt on drug apparent solubility depends on drug physicochemical properties. Drug ionization (compendial media: negative effect, VIP = 2.8, biorelevant media: negative effect. VIP = 2.0) and drug aqueous solubility (compendial media: negative effect, VIP = 1.9, biorelevant media: negative effect, VIP = 2.8) were influential variables in both sets of media. These variables reveal that the slow dissolution of MgSt from powder surface [55] becomes the rate limiting step for the dissolution of highly ionized and/or highly soluble drugs. Drug lipophilicity was a significant variable in both models with different extent in compendial (positive effect, VIP = 1.6) and biorelevant media (negative effect, VIP = 1.8), indicating that the decrease in the apparent solubility of lipophilic drugs by MgSt presence will be pronounced in biorelevant conditions. The pronounced decrease in the solubility of lipophilic drugs by MgSt presence in biorelevant media at 24 hours can be explained by the improved solubilization of lipophilic molecules due to the presence of bile salts [53, 60] which results in the presence of more MgSt particles on the surface of the powder. The impact of MgSt on drug apparent solubility relates also to excipient properties according to the sets of media used. Excipient CRS was a significant variable in the compendial model (negative effect, VIP = 1.1) and reveals that the improved lubrication efficiency of crystalline MgSt hinders powder wettability [17, 61]. Excipient CRS was not significant in biorelevant media, as potentially lubricated particles can be solubilized by the presence of bile salts [53, 60]. Excipient level (negative effect, VIP = 0.9) was a critical variable in the biorelevant model revealing that the enhanced drug solubilization in biorelevant media [53, 60], results in saturation of the powder surface with more MgSt particles when excipient level is increased. Medium characteristics (gastric or intestinal conditions) are critical on the impact of MgSt on drug solubility in biorelevant media, as indicated by the significance of the variable medium (negative effect, VIP = 0.8) in the model. The presence of bile salts in high amounts in the biorelevant basic medium leads to enhanced powder wettability [53] and saturation of powder surface by excipient particles, as explained above.

The impact of MgSt variability on drug apparent solubility relates to drug physicochemical properties, as demonstrated by the significance of certain interactions in the studied models. In compendial media, CRS*solubility (negative effect, VIP = 1.2) and CRS*lipophilicity (positive effect, VIP = 0.9) were significant variables in

the model indicating that the reduction in drug solubility at 24 hours by presence of crystalline MgSt brands will be more pronounced for highly soluble less lipophilic drugs. In biorelevant media, PSD*lipophilicity (negative effect, VIP = 0.9) and PSD*solubility (negative effect, VIP = 0.9) were significant interactions in the model indicating that the high particle size brands will significantly reduce the apparent solubility of highly soluble and/or highly lipophilic drugs. CRS*solubility (negative effect, VIP = 0.9) and CRS*lipophilicity (positive effect, VIP = 1.0) were also significant interactions in the biorelevant model revealing that the decrease in drug solubility at 24 hours by crystalline MgSt brands will be pronounced for highly soluble hydrophilic drugs. An interplay between excipient properties was observed in compendial media by the significance of CRS*PSD (positive effect, VIP = 1.2) in the model. As MgSt brands of lower crystallinity have low lubrication efficiency, decreasing MgSt particle size will be critical only for crystalline brands leading to higher reduction in drug apparent solubility compared to high PSD brands.

2.3.4. Road map of MgSt effects on drug apparent solubility

The roadmap categorizing the excipient REs on drug solubility at 24 hours according to excipient and drug properties is presented in **Figure 2.11** (cases where increased drug solubility was caused by a potential shift in the pH of the solution were not considered).

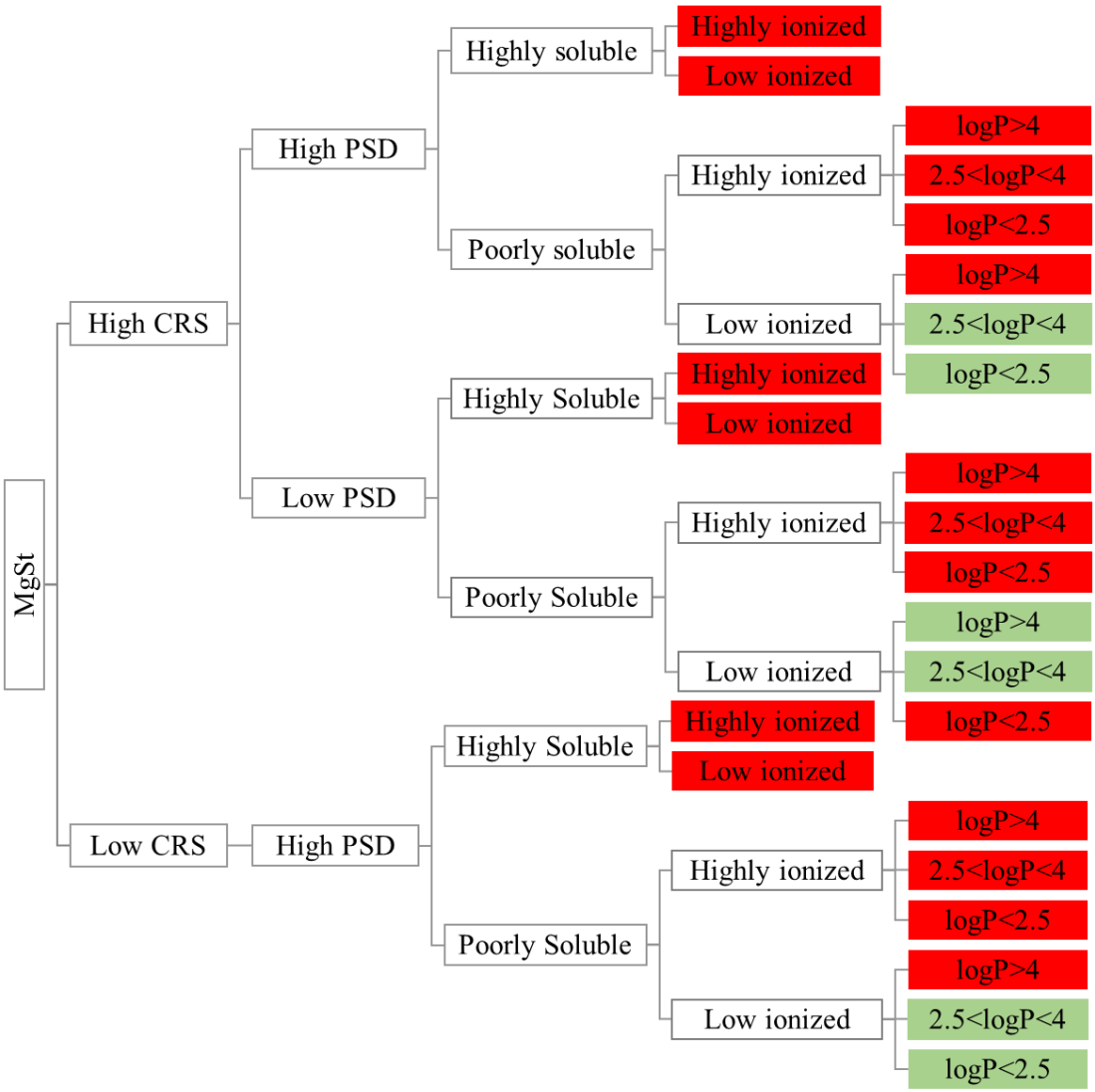


Figure 2.11: Road map of the effects of the studied excipients on drug solubility at 24 hours. Red boxes and green boxes indicate significant and insignificant changes in drug solubility by excipient presence, respectively.

The impact of MgSt on drug apparent solubility relates to drug physicochemical characteristics. Significant changes in drug solubility at 24 hours by MgSt can be anticipated for highly soluble drugs, irrespective of drug ionization state (low or highly ionized). The effects of the studied MgSt brands on the solubility of poorly soluble drugs at 24 hours depend on the state of drug ionization, as significant changes in drug solubility by MgSt presence can occur when poorly soluble drugs are highly ionized irrespective of their lipophilicity. For poorly soluble/low ionized drugs, MgSt is not expected to significantly affect drug apparent solubility, except from the case of

lipophilic drugs (log P > 4) in presence of MgSt brands of high PSD. The construction of the roadmap reveals that excipient selection or change needs to be thoroughly considered as excipient variability may be problematic for oral drug performance.

2.4. Conclusion

Presence of excipients and excipient variability in oral dosage forms can affect product performance. MgSt is a commonly used lubricant in immediate release formulations but it can compromise drug dissolution. The current study focused on identifying the biopharmaceutical implications of MgSt presence and variability on drug apparent solubility. Solubility studies showed that for the majority of cases, presence of MgSt significantly decreased drug solubility at 24 hours due to its hydrophobic nature. The extent of the changes in drug apparent solubility depended on the material attributes of the studied MgSt brands, with excipient CRS and PSD being the most influential. The complex nature of excipient variability was revealed as the effects of excipient properties on drug solubility at 24 hours strongly related to drug physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and medium characteristics (pH/presence of bile salts). The use of multivariate data analysis and the construction of roadmaps allowed the identification of cases where MgSt presence or variability could be challenging for oral absorption. This systematic investigation demonstrates the high criticality of MgSt as risks for oral product performance and drug absorption could be anticipated when varying MgSt properties.

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Chapter 2 Commentary

Magnesium stearate (MgSt) is a commonly used lubricant in oral solid dosage forms but it can delay drug dissolution as it acts as water repellant. In this chapter, the impact of MgSt variability and variation on drug apparent solubility in a biopharmaceutical perspective using compendial and biorelevant media was presented. Three MgSt brands (MgSt-BDH, Ligamed MF-2-V, Ligamed MF-3-V) of different grades and/or suppliers were selected and characterized to identify differences in their critical material properties. Differences in excipient crystallinity, particle size distribution (PSD) and specific surface area (SSA), that could potentially affect oral drug performance, were identified. Presence of MgSt was found to decrease the apparent solubility of the majority of compounds due to its hydrophobic nature. The reduction in drug solubility at 24 hours by MgSt was more pronounced for highly ionized and/or hydrophilic highly soluble drugs, due to the fast saturation of the powder surface with MgSt particles. MgSt brands of higher crystallinity or smaller particle size resulted in pronounced reduction in drug solubility as well due to their better lubrication efficiency. The statistical evaluation revealed that drug physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and excipient critical material attributes (crystallinity, PSD) were the most influential factors affecting the impact of MgSt on drug apparent solubility. The criticality of MgSt presence and variability for oral drug performance was classified with the construction of roadmaps. It is concluded that presence of MgSt or changes in MgSt critical material attributes can be crucial for oral drug bioavailability and that excipient selection need to be thoroughly considered during formulation development.

Chapter 3 Preface

Changes in excipient material properties or excipient amount in oral solid dosage forms may affect final product quality leading to batch failures or modifying drug bioavailability. Hypromellose (HPMC) is a polymeric excipient used as a binder (in low levels) or as release controlling agent (in high levels) in oral solid dosage forms. The formation of a viscous layer around particles by HPMC presence can delay drug release. Numerous studies have demonstrated that changes in the properties of HPMC (molecular weight, degree of substitution, substitution pattern, particle size distribution, level) can affect drug dissolution and release. Varying HPMC brands in pharmaceutical formulations can influence product performance, even in cases where the studied brands were considered equivalent. In addition, the ability of HPMC to form a viscous layer depends on several gastrointestinal factors, as revealed in Chapter 1. Understanding therefore the effects of HPMC of varying properties on oral drug performance in a systematic approach is beneficial and would facilitate excipient implementation in the Quality by Design (QbD) approaches. This chapter focuses in examining the biopharmaceutical implications of HPMC variability and variation on drug apparent solubility. The use of multivariate data analysis and the construction of roadmaps will allow the identification of the potential risks of HPMC presence and variability for oral product performance. The results from this chapter will be considered as a part for the creation of a data set where excipient presence and variability are critically evaluated in biorelevant terms.

Chapter 3. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties. Case study: Hypromellose (HPMC)

Abstract

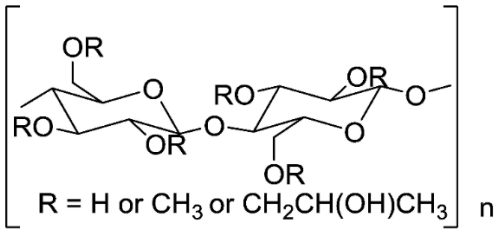
Identification of the biopharmaceutical risks of excipients and excipient variability on oral drug performance can be beneficial for the development of robust oral drug formulations. The current study investigated the impact of Hypromellose (HPMC) presence and varying viscosity type on the apparent solubility of drugs with wide physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility). The role of gastrointestinal conditions on the impact of excipients on drug apparent solubility was assessed with the use of pharmacopoeial (compendial) and biorelevant media. Presence of HPMC affected drug apparent solubility according to the physicochemical properties of studied compounds. Drug shielding or the formation of a viscous layer by the excipient on the powder surface reduced the solubility of highly soluble and/or highly ionized compounds and was more pronounced mainly at early time points. Increase in the apparent solubility of poorly soluble low ionized drugs containing a neutral amine group was observed which may relate to enhanced drug solubilization or reduced drug aggregation. The use of multivariate data analysis and the design of roadmaps (combining the effects of HPMC on drug solubility at 24 hours to excipient viscosity and drug physicochemical properties) confirmed the importance of drug physicochemical properties on the impact of excipients on drug apparent solubility and revealed that changes in the excipient material attributes or excipient amount may not be critical for oral drug performance when HPMC is used as a binder.

Keywords: excipient variability, HPMC, viscosity, drug solubility, physicochemical properties

3.1. Introduction

Presence of excipients in oral solid dosage forms is a topic of great interest in terms of pharmaceutical Quality by Design (QbD). Further to their intended use, excipients may affect the properties and performance of final dosage forms leading to batch inconsistencies, altered bioavailability and bioinequivalence of products [1-3]. Excipient variability (changes in material properties) and variation (changes in amount) constitutes an additional obstacle to robust manufacturing, as changes in excipient material properties can undermine the critical quality attributes of the final product [4]. Moreover, excipient inertness is questionable as their presence can influence oral drug absorption [5, 6].

Binders are typically used in solid dosage form manufacturing to promote adequate mechanical strength of granules or tablets. Hypromellose, also called hydroxypropyl methylcellulose (HPMC), is a polymeric binder used in wet granulation [7]. HPMC is a water soluble nonionic cellulosic polymer substituted with methoxy and hydroxypropyl groups (**Figure 3.1**). In addition to its binding properties, HPMC is extensively used as a release controlling excipient. This dual functionality depends on excipient level (2% w/w – 5% w/w as binder and 10% w/w - 80% w/w as release modifier) and viscosity type (high viscosity grades are typically used to control drug release) [8]. The effectiveness of HPMC can be influenced by its swelling and gelling properties which can delay drug dissolution or release [9, 10].



Hypromellose

Figure 3.1: Chemical structure of Hypromellose (ChemDraw Professional 15.0).

Molecular properties (molecular weight, degree of substitution, substitution pattern), particle properties (particle size distribution) and excipient level have been identified as critical material attributes affecting excipient and product performance [4]. Molecular weight and excipient level directly relate to the formation of a viscous HPMC gel layer. HPMC brands of high molecular weight swell faster and form a

thicker viscous layer compared to low molecular weight brands [9, 11, 12]. The formation of thick viscous layers when increasing HPMC molecular weight is attributed to the slow rate of polymer erosion [9]. Real-time surface dissolution UV imaging demonstrated the complex polymeric network formed by high molecular weight HPMC brands and the susceptibility of low molecular weight HPMC brands to erosion [13]. Due to the proportionality of HPMC molecular weight and viscosity of HPMC aqueous solutions, high molecular weight HPMC brands correspond to high viscosity HPMC types. The formation and thickness of the gel layer depends also on the level of HPMC in solid dosage forms. Increasing the level of HPMC results in a concentrated and viscous gel layer either due increased chain entanglement [14] or slow polymer erosion rate [15]. A minimum excipient concentration (referred to as excipient percolation threshold) under which HPMC cannot form an effective viscous layer able to control drug release was reported [16]. The percolation thresholds of different viscosity type HPMC brands were similar (20% v/v corresponding to 20% w/w) and showed consistent controlled drug release (verapamil HCl, USP 2 apparatus, 50 rpm, 900 mL, phosphate buffer pH 7.5) from extended release tablets containing HPMC [16]. Use of confocal laser scanning microscopy revealed that the early gel layer formation depends on the level of HPMC. Hydrophilic matrices containing 5% w/w and 10% w/w of HPMC, formed a thin and heterogeneous gel layer initially (5 – 15 min), which could not be maintained due to the increased water uptake accelerating polymer erosion [17].

Several biopharmaceutical factors affecting the impact of HPMC on product performance have been identified. The impact of the viscous HPMC gel layer on drug release relates to drug characteristics. Highly soluble drugs are released by diffusion through the matrix while poorly soluble drugs by erosion of the matrix [9]. The performance of HPMC depends on the composition and properties of the dissolution medium. Salts [18], sugars [19] and food components [20] interact with the polymeric chains of HPMC and affect the formation of the gel layer. Detailed representation of the impact of the aforementioned factors on the excipient performance were provided in Chapter 1. Moreover, bile salts were found to affect the thermal transition (gel formation) of cellulosic polymers. The hydrophobic parts of bile salts adsorb onto the hydrophobic regions of polymers and increase the excipient transition temperature upon heating [21, 22]. The pH of the dissolution medium can also affect the

swelling/gelling properties of HPMC due to changes in the transport behaviour of water into the polymer, despite the non-ionic nature of HPMC. Rapid polymer hydration and larger excipient swelling was observed in media of basic (24% increase in polymer diameter after 200 min at pH = 6) compared to acidic pH (15% increase in polymer diameter after 200 min at pH = 2). The authors highlighted the biopharmaceutical consequence of this polymeric response as faster drug release should be expected in the acidic gastric compared to the basic intestinal compartment [23].

The aim of this study was to assess the biopharmaceutical impact and criticality of HPMC variability and variation (when used as a binder in immediate release formulations) on drug apparent solubility. HPMC variability and variation were addressed by selecting three HPMC brands of different viscosity type using two different excipient levels (low: 2% w/w, high: 5% w/w). The biopharmaceutical implications of HPMC variability on drug apparent solubility were examined by choosing compounds of a wide range of physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and media (compendial and biorelevant) simulating the gastrointestinal conditions. Multivariate data analysis (Partial Least Squares (PLS)) and roadmaps were used to identify the critical role of certain variables (drug properties, excipient presence, medium characteristics) on the impact of HPMC on drug apparent solubility.

3.2. Materials and Methods

3.2.1. Materials

APIs: Sulfamethoxazole and paracetamol were obtained from Fisher Scientific (UK). Furosemide, itraconazole and dipyridamole were obtained from VWR (UK). Ibuprofen, carbamazepine and metformin were obtained from Fagron (UK). Excipients: HPMC-Sigma was obtained from Sigma Aldrich (UK). Pharmacoat 606 and Pharmacoat 615 were obtained from Shinetsu (Japan). Chemicals: Acetic acid (>99.7%), hydrochloric acid 36.5–38%, HPLC grade methanol, HPLC grade acetonitrile, dichloromethane, pepsin (from porcine) were obtained from Sigma-Aldrich (UK). Maleic acid, sodium chloride, sodium hydroxide, potassium phosphate monobasic, sodium dihydrogen orthophosphate dihydrate, disodium hydrogen orthophosphate dihydrate, potassium dihydrogen orthophosphate, anhydrous sodium sulfate, HPLC grade trifluoroacetic acid were obtained from Fisher Scientific (UK).

Sodium taurocholate (Prodotti Chimici Alimentari S.P.A., Italy), egg lecithin – Lipoid EPCS (Lipoid GmbH, Germany), were obtained from the sources specified. Water was ultra-pure (Milli-Q) laboratory grade. Filters: Whatman® 13 mm cellulose nitrate filters 0.45 μm pore size and polytetrafluoroethylene (PTFE) 13 mm filter 0.45 μm pore size were purchased from Fisher Scientific (UK).

3.2.2. Instrumentation

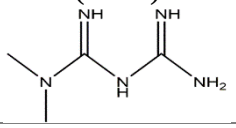
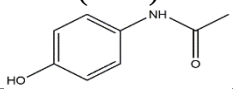
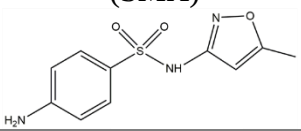
Fisherbrand waterbath (Fisher Scientific, UK), Sartorius BP 210 D balance (Sartorius Ltd, UK), Buchi R114 Rotavapor (Buchi, Switzerland), Mettler Toledo SevenCompact S210 pH meter (Mettler Toledo, Switzerland), Vortex-Genie 2 vortex mixer (Scientific Industries Inc, USA), Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A), autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector (G1329A) and Chemstation software (Agilent Technologies, USA)

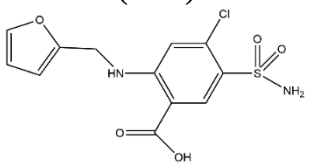
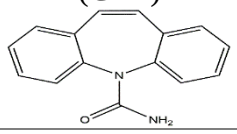
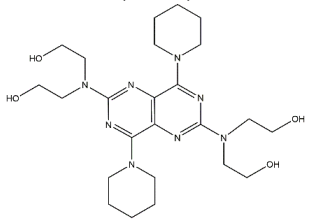
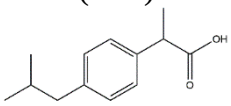
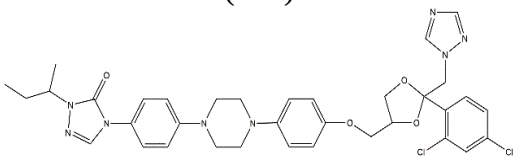
3.2.3. Methods

3.2.3.1. Compounds selected for solubility experiments

The compounds used for the solubility experiments and their physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) were presented in **Table 3.1**.

Table 3.1: Physicochemical properties and structure of the compounds used for the solubility experiments. (ChemDraw Professional 15)

Drug	Ionization	Lipophilicity (log P)*	Solubility
Metformin (MTF) 	Weak base (pKa=2.8) [24]	-0.5[a]	High [24]
Paracetamol (PRC) 	Neutral (pKa=9.38) [25]	0.46[a]	High [25]
Sulfamethoxazole (SMX) 	Weak acid (pKa_1=1.7, pKa_2=5.6) [26]	0.89[a]	Low [27]

Furosemide (FRS) 	Weak acid (pKa=3.8) [28]	2.29 [28]	Low [28]
Carbamazepine (CBZ) 	Neutral (pKa=15)[a]	2.45[a]	Low[a]
Dipyridamole (DPL) 	Weak base (pKa=6.2) [29]	2.74 [30]	Low [31]
Ibuprofen (IBU) 	Weak acid (pKa=4.5) [32]	3.97[a]	Low [32]
Itraconazole (ITZ) 	Weak base (pKa=4.5) [33]	5.66[a]	Low [34]

*Experimental values

[a]Source: DrugBank

3.2.3.2. Media prepared for solubility experiments

Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to the method described in the United States Pharmacopeia [35]. Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF-V2) were prepared as per literature references [36].

3.2.3.3. Design of Experiments (DoE) used for solubility experiments

A full-factorial Design of Experiments (DoE) was performed to determine the number of necessary experiments using StatGraphics Centurion XVII (Statpoint Technologies Inc, USA). As drug solubility will differ according to the composition of the studied media (pH, presence of bile salts), two models for the DoE were

constructed to discriminate between the effects of excipients on drug apparent solubility in compendial (Model 1) and biorelevant conditions (Model 2). The examined factors were: i. compound (**Table 3.1**), ii. excipient brand (Pharmacoat 606, Pharmacoat 615, HPMC-Sigma), iii. excipient level (low, high), iv. medium (gastric, intestinal). The impact of each excipient on drug apparent solubility [expressed as the relative increase or decrease in drug solubility in presence compared to absence of excipient (Section 3.2.3.5)] was set as the response. A total of 96x3 experiments was determined for each model. 16x3 additional experiments for each model were conducted to determine drug apparent solubility in the corresponding media in the absence of excipient. These experiments were not included in the DoE as drug solubility in excipient absence was measured only for the calculation of relative excipient effects on drug solubility.

3.2.3.4. Solubility studies

Drug solubility studies in the absence and presence of excipient were performed in triplicate using the shake-flask method [37]. Drug excess and 2% w/w or 5% w/w of each excipient were weighed and placed in centrifuge tubes. The amount of excipient was determined as follows: i. for poorly soluble drugs, considering an average of 500 mg tablet weight [38] (which resulted in 9% w/w (low level) and 20% w/w (high level) of excipient in the total volume of the physical mixture) and ii. for highly soluble drugs, according to the amount of drug excess and the relative ratio of drug-excipient based on point (i). The physical mixtures were vortexed for 3 minutes. 5 mL of each medium were added in the tubes and the samples were placed in a shaking water bath (37 °C, 200 strokes per minute (spm)). At 0.5, 4 and 24 hours (for PRC, SMX, CBZ, DPL, IBU) and 24 hours (for MTF, FRS, ITZ), 500 μL were sampled and filtered through PTFE filters (or cellulose nitrate filters for the cases of IBU and CBZ). Filter adsorption studies were prior performed in triplicate for each drug. No adsorption issues onto the filters used were observed for the studied drugs. Filtered samples were further diluted (if needed) with the corresponding medium and analysed by HPLC (**Table 3.2**). Analytical procedures for drug quantification in the samples were modifications of already published methods. Drug quantification was made based on calibration curves. Standards were formulated from concentrated stock solutions consisting of drug dissolved in MeOH. As changes in the pH of solutions by presence of dissolved drug [31] may affect drug solubility, the pH of samples after the

completion of each experiment was measured. Drug apparent solubility was calculated based on the sample drug concentration measured. Solubility values measured experimentally in excipient absence for neutral drugs, for weak acids in acidic media and for weak bases in basic media determined the intrinsic solubility values. Solubility values measured experimentally in excipient absence in basic media (for weak acids) and acidic media (for weak bases) determined drug apparent solubility of the ionized molecules.

Table 3.2: HPLC methods used for drug quantification

	Column	Mobile Phase	Flow Rate (mL/min)	Temp (°C)	Inj. Vol. (µL)	Detection wavelength (nm)	R_t (min)	Concentration of stock solutions (mg/mL)	Calibration range in acidic media (µg/mL)	Calibration range in basic media (µg/mL)	Reference
MTF	Inertsil Phenyl (Metachem) 250x3mm - 5µm	MeOH/Phosphate buffer pH 7 (70:30)	1	20	20	236	8	2	10 - 200	10 - 200	[39]
PRC	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (20:80)	1	20	20	257	6	2	10 - 200	10 - 200	[40]
SMX	Polaris (Metachem) C18 250x4.6mm – 5µm	MeOH/Phosphate buffer pH 6.8 (20:80)	1	25	20	257	7	1	10 - 200	50 – 500	[41]
FRS	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/water with 0.1% formic acid (50:50)	1	25	50	232	4	1	2 – 20	10 - 200	[42]
CBZ	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (60:40)	1	25	100	285	4	1	10 – 150	10 - 150	[43]
DPL	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/water with 0.1% TFA (30:70)	1	25	50	284	6	1	10 -200	Compendial 1 - 5 Biorelevant 2 - 10	[44]
IBU	Eclipse XDB-C18(Agilent) 250x4.6mm – 5µm	MeOH/water with 0.2% acetic acid (65:35)	1	25	100	233	6	1	5 – 40	10 - 200	[45]
ITZ*	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/phosphate buffer pH 3 (60:40)	1	20	100	Emission: 252 Excitation: 360	8	0.1	Compendial 0.5 – 5 Biorelevant 0.1 - 10	0.015 – 0.06	[46]

*Quantification was made using HPLC-Fluorescence

3.2.3.5. Treatment of *in vitro* solubility data

The Relative Effect (RE) of each excipient on drug apparent solubility was calculated based on equation 3.1:

$RE = \frac{(S-Sr)}{Sr}\ x\ 100$ (Equation 3.1)

where S and Sr denote drug solubility in presence and absence (reference solubility) of excipient at 0.5, 4 and 24 hours. REs of excipients on drug apparent solubility > 25% or < -20% were considered as significant change in drug apparent solubility to assess excipient criticality (this range was selected as a similar range is set in order to assess differences in drug exposure after oral administration; i.e. in bioequivalence studies) [47].

Box plots depicting the impact of excipients on drug solubility at 24 hours for all the studied compounds or as a function of time (0.5, 4 and 24 hours) for CBZ and DPL were constructed using Spotfire 7.10.1 (TIBCO software Inc, USA). The classification gradient maps portraying the impact of the studied brands on drug solubility at 24 hours as a function of drug aqueous solubility were generated using SigmaPlot 13.0 (Systat Software Inc, USA). For the construction of 3D mesh plots depicting the impact of excipients on drug apparent solubility as a function of time and drug ionization, solubility data for PRC, SMX, IBU, DPL were smoothed via the negative exponential technique to allow better visualization using SigmaPlot 13.0 (Systat Software Inc, USA).

In cases where drug intrinsic solubility was not determined experimentally, the theoretical intrinsic solubility was calculated using the solubility-pH equations (Equations 3.2-3.5) [48]:

$\log S = \log S_o + \log(10^{-pKa+pH} + 1)$ for weak acids (Equation 3.2)

$\log S = \log S_o + \log(10^{pKa-pH} + 1)$ for weak bases (Equation 3.3)

$\log S = \log S_o + \log(10^{+pKa_2+pKa_1-2pH} + 10^{pKa_2-pH} + 1)$ for diprotic bases (Equation 3.4)

$\log S = \log S_o + \log(10^{+pKa_1-pH} + 10^{-pKa_2+pH} + 1)$ for ampholytes (Equation 3.5)

where S and S_o indicate drug solubility at the given pH and the intrinsic solubility, respectively. The final pH and experimental solubility values of the ionized drug in basic (for weak acids) or acidic media (for weak bases) were used for the calculation of the theoretical intrinsic solubility. Theoretical pH-solubility profiles in the physiological pH range were constructed to assess if changes in the pH of the medium could justify differences in drug apparent solubility by excipient presence. The final pH and intrinsic solubility values (experimental or theoretical) were used for the construction of the theoretical pH – solubility profiles in the physiological pH range based on Equations 3.2 -3.5.

3.2.3.6. Multivariate Analysis of solubility data

Excipient REs on drug apparent solubility were correlated to drug physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility), excipient critical material attributes (viscosity, level) and medium characteristics (gastric, intestinal) by partial least squares (PLS) regression using the XLSTAT software (Microsoft, USA). Two models for the REs of excipients on drug solubility in compendial media (Model 1) and biorelevant media (Model 2) were constructed. The evaluated variables for both models were categorized according to their type as categorical (expressing a category or type) and numerical (measurements with numerical meaning). Categorical variables included: i. drug solubility (poor, high), ii. amine group (absence, presence), iii. excipient level (low, high), iv. medium (gastric, intestinal) while numerical parameters included: i. % of drug ionized (F_{ion}; calculated based on the Henderson – Hasselbalch equation at the pH of each medium), ii. drug lipophilicity (log P), iii. excipient viscosity (cP). Excipient REs on drug solubility at 24 hours were used as the response. The selected interaction terms included each excipient property combined with each drug physicochemical property (drug ionization, drug lipophilicity, drug aqueous solubility) and medium characteristics (gastric, intestinal). Observation diagnostics were performed prior to model analysis to identify outliers in the data set. The distance of each observation to the model in the Y-plane (DmodY) tool based on PLS residuals was used. Plots of standardized DmodY vs each observation were generated and any observation exceeding the maximum tolerance volume in Y ($D_{crit(Y)}$) was considered an outlier [49, 50]. Exclusion of outliers was based on: i. deviating cases (positive REs) in solubility caused by a shift in the pH of the solution, ii. observations resulting in high variability

(coefficient of variation (CV%) > 20%) within the triplicate samples (one value from the triplicate could be excluded as the outlier analysis could detect these values). PLS models generated with and without outlier exclusion (data not shown) confirmed that outlier exclusion did not alter the interpretation of results but only enhanced the predictive ability of the regression model. The generated models were assessed in terms of goodness of fit (R^2) and goodness of prediction (Q^2). High values of R^2 and Q^2 with a difference not greater than 0.2 - 0.3 were indications of successful models [51]. The number of PLS components (lines on the X-space which best approximate and correlate with the Y-vector) was based on minimum predictive residual sum of squares (PRESS) [51]. From the available components the one at which Q^2 reached its maximum value was selected [49]. Standardized coefficients were used to show the direction (positive or negative) and extent of each variable on the response. The significance of the variables was assessed by the variable influence on projection (VIP) value. VIP values > 0.8 were considered as moderately influential in the model while VIP values > 1 were considered the most influential in the model [51]. A 95 % confidence interval was used.

3.2.3.7. Roadmap Design

A roadmap design for identifying potential biopharmaceutical risks of HPMC variability on drug apparent solubility was constructed by combining the impact of excipients on drug solubility at 24 hours from the solubility studies to excipient (viscosity) and drug (drug ionization, drug lipophilicity, drug aqueous solubility) physicochemical properties. Drug were categorized according to drug aqueous solubility and drug lipophilicity (**Table 3.1**) and drug ionization (low ionized: $F_{(ion)}$ < 50%, highly ionized: $F_{(ion)}$ > 50%). The risk assessment of the impact of excipients on drug apparent solubility was evaluated by setting reference range criteria of -20% - 25% [47] on the REs of excipient on drug solubility at 24 hours. REs of excipients on drug solubility outside these values (REs < -20% or REs > 25%) were considered critical for oral drug performance.

3.3. Results and Discussion

3.3.1. Properties of HPMC

Based on product specifications and certificates of analysis, differences in terms of viscosity (cP) for the studied HPMC brands were identified. Pharmacoat 606 (6 cP)

and Pharmacoat 615 (15 cP) are low viscosity brands compared to HPMC-Sigma (3500 – 5600 cP). The studied polymers belong to the same category of substitution type 2910 (28% – 30% of methoxy and 7% - 12% hydroxypropoxyl content).

3.3.2. Solubility studies

3.3.2.1. Impact of the studied HPMC brands on drug apparent solubility

The reference solubility values of the studied compounds at 24 hours in compendial and biorelevant media are summarized in **Table 3.3**. For neutral drugs, the reference solubility did not depend on the pH of the studied media (as expected) but on the presence of solubilizing components, as increased reference solubilities were observed in biorelevant compared to compendial media due to the presence of bile salts [52]. Different reference solubility values within acidic and basic media were observed for weak acids (SMX, FRS, IBU) and weak bases (DPL, ITZ) due to their ionization pattern, except from the case of MTF as drug was fully ionized in all the studied conditions [24]. SMX was ionized in both acidic and basic media due to its two pKa constants, as explained in Chapter 2. The impact of bile salts on drug solubility was demonstrated for weak acids/weak bases in media where drugs were unionized (higher solubility values in biorelevant compared to compendial media) [52]. For weak acids/weak bases (except from the case of MTF) in media where drug are highly ionized, drug solubility values were higher in compendial (0.1 N HCl pH 1, phosphate buffer pH 6.8) compared to biorelevant media (FaSSGF pH 1.6, FaSSIF-V2 pH 6.5), as pH has a greater impact on drug solubility compared to bile salts [53].

Table 3.3: Reference solubility values (μg/mL) of the studied drugs at 24 hours in compendial and biorelevant media. (Mean ± SD, n = 3)

Drug	Compendial Media		Biorelevant Media	
	0.1 N HCl pH 1	Phosphate buffer pH 6.8	FaSSGF	FaSSIF-V2
MTF	3.1×10^5 ($\pm0.3\times10^5$)	3.1×10^5 ($\pm0.2\times10^5$)	3.4×10^5 ($\pm0.8\times10^5$)	4.3×10^5 ($\pm0.4\times10^5$)
PRC	1.6×10^4 ($\pm0.1\times10^4$)	1.5×10^4 ($\pm 0.1\times10^4$)	1.7×10^4 ($\pm 0.2\times10^4$)	1.7×10^4 ($\pm 0.1\times10^4$)
SMX	1.6×10^3 ($\pm0.1\times10^3$)	3.7×10^3 ($\pm 0.1\times10^3$)	862 (±21)	1.3×10^3 ($\pm 0.1\times10^3$)
FRS	14 (±2)	3.4×10^3 ($\pm1.4\times10^2$)	15 (±1)	1.6×10^3 ($\pm3.0\times10^2$)
CBZ	265 (±6)	227 (±9)	368 (±1)	280 (±7)
DPL	1.3×10^4 ($\pm9.1\times10^2$)	5 (±1)	8.6×10^3 ($\pm2.0\times10^2$)	13 (±1)
IBU	43 (±3)	5.5×10^3 ($\pm 6.7\times10^2$)	44 (± 5)	1.5×10^3 (± 5.8)
ITZ	11 (±1)	-*	1.2 (± 0.2)	0.05 (± 0.01)

*below limit of detection of the analytical method

The effects of the HPMC brands on the apparent solubility of the studied compounds in compendial and biorelevant media are presented in **Figures 3.2** and **3.3**, respectively.

Neutral drugs: Cases of significant decrease in drug solubility at 24 hours by the studied HPMC brands were observed for PRC (Pharmacoat 606: -36% < REs < -20%, Pharmacoat 615: -32% < REs < -22%, HPMC-Sigma: -30% < REs < -22%). Differences in the apparent solubility of neutral drugs in HPMC presence cannot be attributed to the minor changes in the pH of the media (**Figures 3.4**). The pronounced reduction in drug solubility by HPMC at 24 hours is attributed to the slow drug dissolution and/or drug solubilization as excipients with slow dissolution rate may

shield drug particles from the dissolution medium [54] or the formation of a viscous excipient layer on the powder surface [55]. Significant increase in drug apparent solubility by the studied HPMC brands was observed for CBZ in compendial media (Pharmacoat 606: 32% < REs < 50%, Pharmacoat 615: 28% < REs < 33%, HPMC-Sigma: 50% < REs < 60%) and in FaSSIF-V2 (REs of approximately 60% for all the studied brands). Solubility data of CBZ at 0.5, 4 and 24 hours in absence and presence of the studied HPMC brands in compendial and biorelevant media are presented in **Figure 3.5**. The solubility of pure CBZ decreased through time in compendial media (350 μg/mL and 250 μg/mL at 0.5 hours and 24 hours, respectively), potentially due to drug aggregation [56] or due to the solution mediated phase transformation of CBZ from the anhydrate to the dihydrate form [57]. The decrease in CBZ solubility was slower in biorelevant media (FaSSGF: 387 μg/mL to 367 μg/mL at 0.5 hours and 24 hours, respectively, FaSSIF-V2: 307 μg/mL to 280 μg/mL at 0.5 hours and 24 hours, respectively). Reduction in CBZ apparent solubility is not observed in presence of HPMC, as potentially dissolved polymer particles may enhance drug solubilization and delay drug aggregation [58]. Inhibition of the CBZ solution mediated phase transformation by hydrogen bonding [59] or by excipient adsorption in the formed nuclei/crystals delaying the rate of nucleation and crystal growth [57] could also explain the fact that CBZ solubility was not reduced in excipient presence.

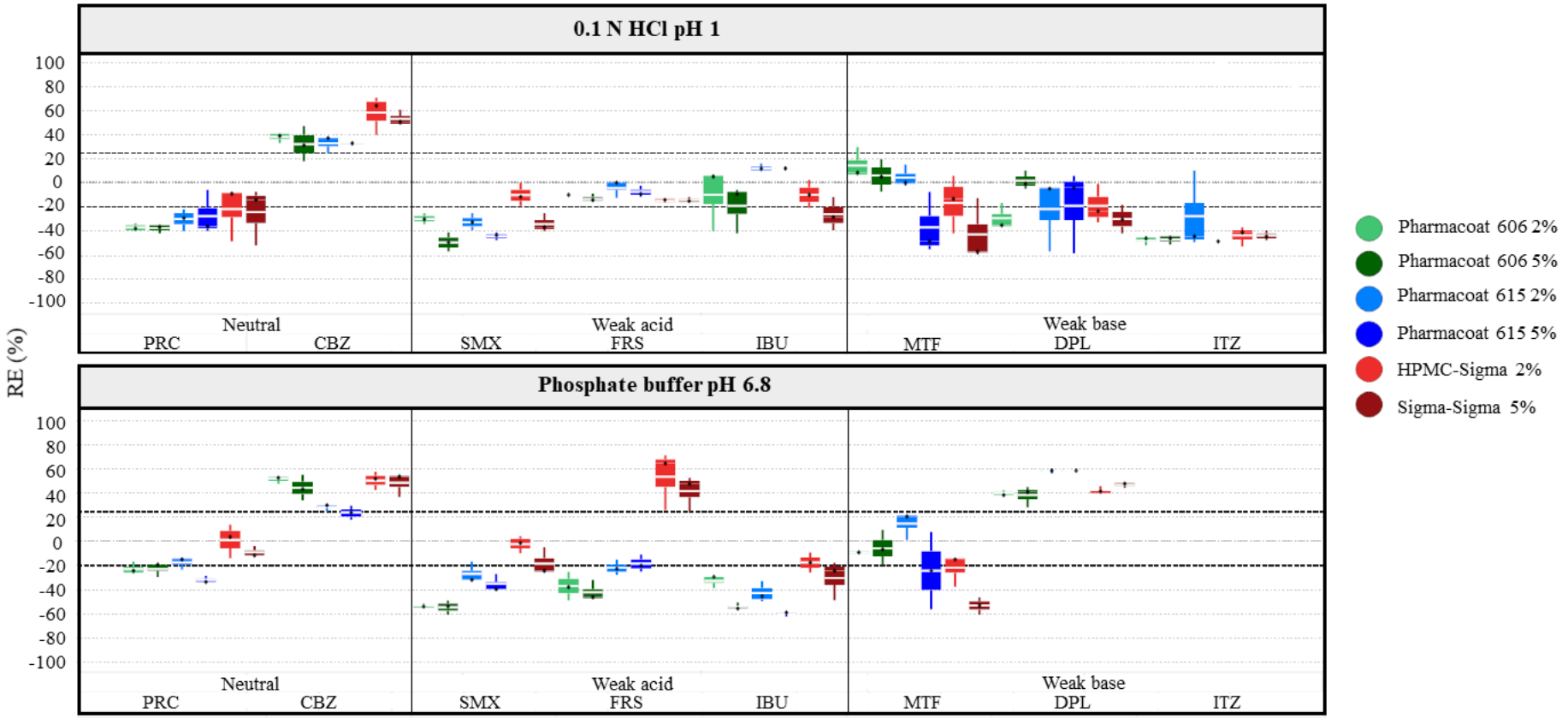


Figure 3.2: Box plots of the relative effects (%) of the HPMC brands on drug solubility at 24 hours in compendial media. The excipient brands are shown as: i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour) and iii. HPMC-Sigma (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

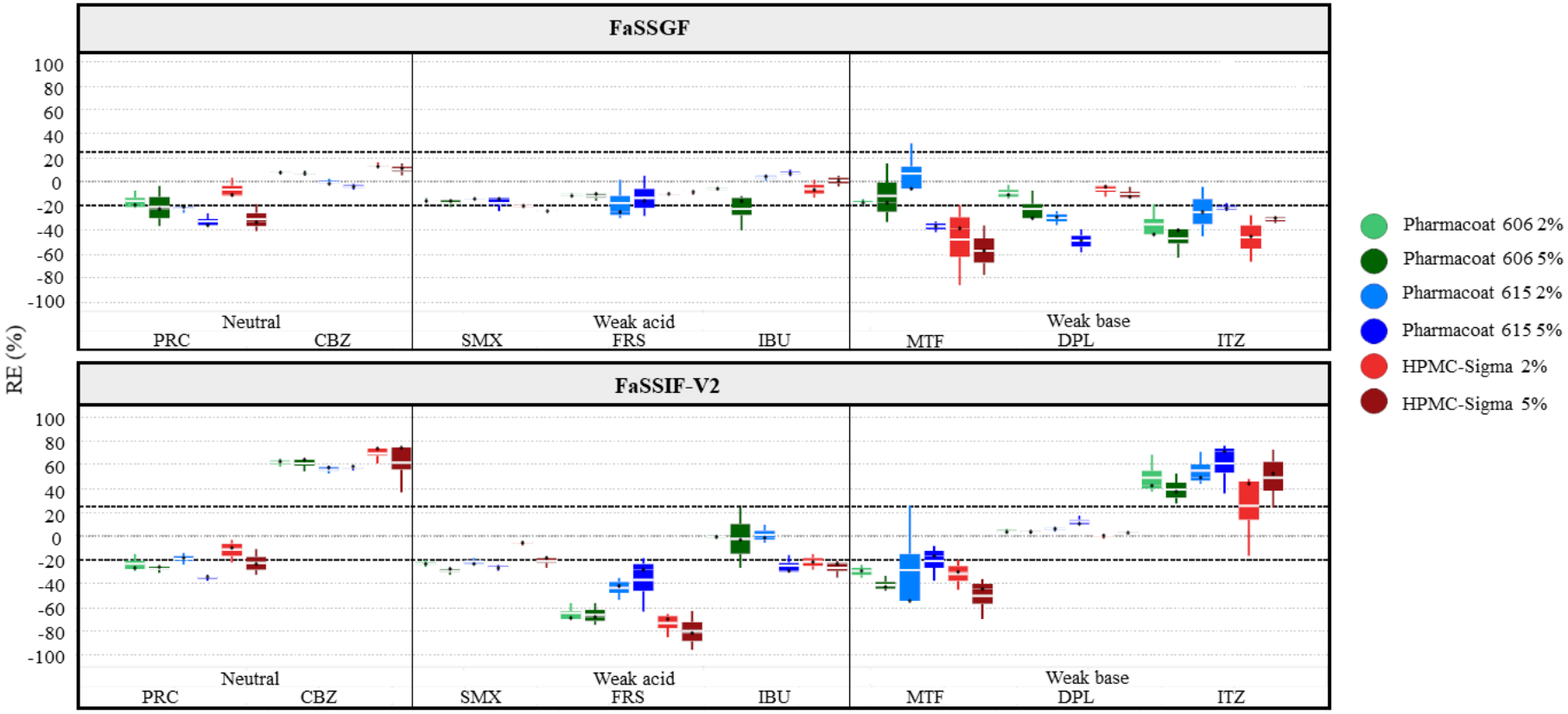


Figure 3.3: Box plots of the relative effects (%) of the HPMC brands on drug solubility at 24 hours in biorelevant media. The excipient brands are shown as: i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour) and iii. HPMC-Sigma (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

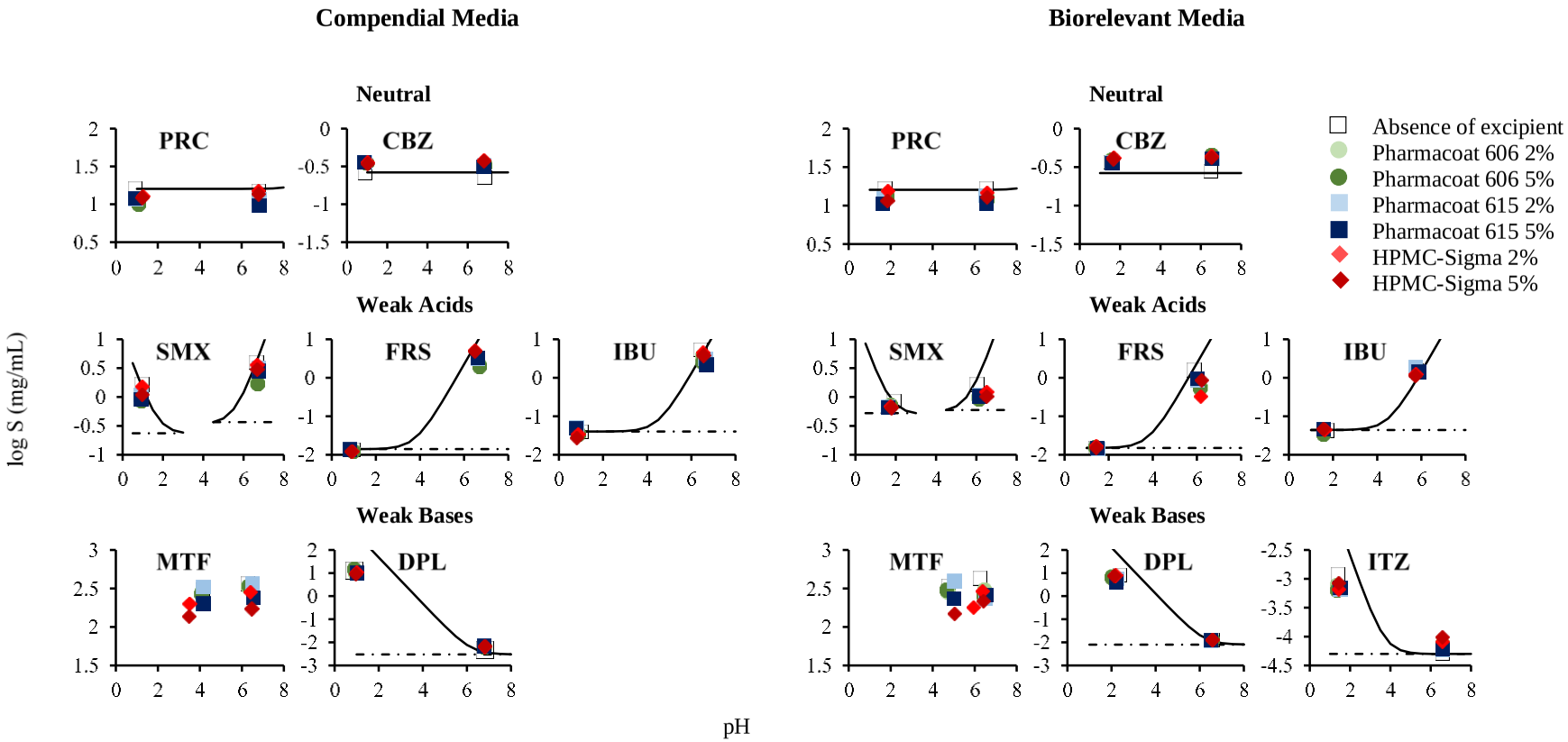


Figure 3.4: Theoretical pH-solubility profiles of the studied drugs in compendial and biorelevant media and experimental drug solubility values in absence (squares) and presence of excipients (i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour), iii. HPMC-Sigma (red colour)). Dashed lines indicate drug intrinsic solubility.

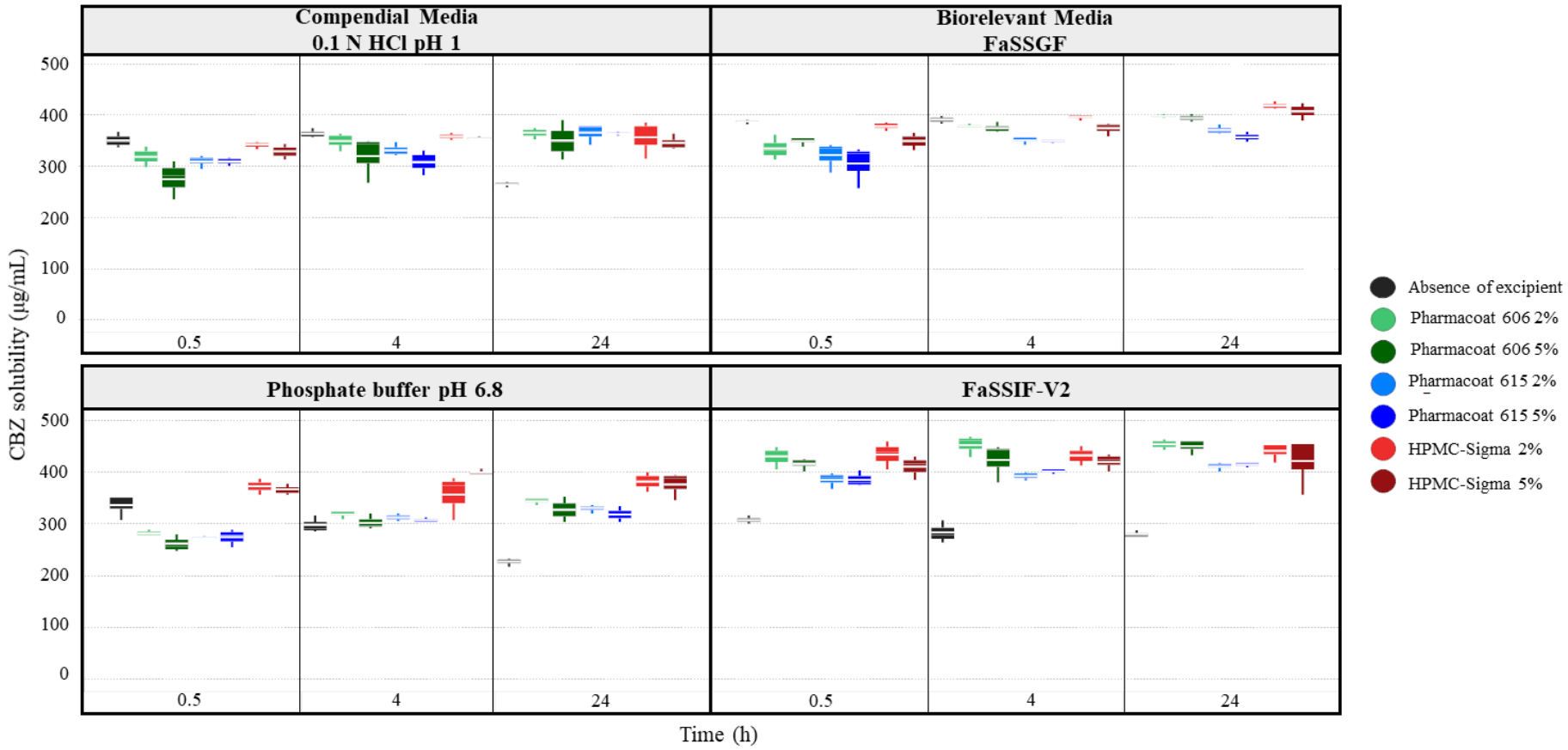


Figure 3.5: Box plots of CBZ solubility (µg/mL) in absence (black colour) and presence of the studied HPMC brands (i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour) and iii. HPMC-Sigma (red colour)) in compendial and biorelevant media. Light and dark colours correspond to low and high excipient level, respectively. (Mean, n = 3)

Weak acids: Significant reduction is observed in weak acidic compound solubility at 24 hours, especially in basic conditions (Pharmacoat 606: -65% < REs < -20%, Pharmacoat 615: -40% < REs < -20%, HPMC-Sigma: -80% < REs < -20%). The studied HPMC brands, also significantly decreased SMX solubility in 0.1 N HCl pH 1 (-50% < REs < -30%) at 24 hours (**Figures 3.2 and 3.3**). In the cases of significant reduction in drug apparent solubility by HPMC presence, small changes in the pH of acidic media occurred in absence or presence of excipient (± 0.1 pH units) while the pH of basic media in absence or presence of excipient decreased (0.2 – 0.7 pH units) (potentially due to the dissociation of weak acids). The experimental solubility values in excipient presence at 24 hours were lower compared to theoretical ones (expected by the change in the pH of the media) (**Figure 3.4**). As the pronounced reduction in drug apparent solubility by HPMC cannot be explained by the shift in the pH of the media, it is attributed to the delay in drug dissolution and/or drug solubilization, as explained previously in the case of neutral drugs. Significant increase in drug solubility at 24 hours was only observed for FRS in presence of both levels of HPMC-Sigma in phosphate buffer pH 6.8 (REs of 53% and 41% for the low and high level, respectively). Differences in the pH of the medium in presence (reduction of 0.3 pH units) and absence of excipient (reduction of 0.2 pH units) were observed. Evaluation of the theoretical pH-solubility profile reveals that drug solubility in absence of excipient does not correspond to the theoretical drug solubility (expected according to the change in the pH of the medium). In presence of HPMC-Sigma, the experimental and theoretical solubility values are similar, therefore the increase in drug solubility at 24 hours in presence of HPMC-Sigma is attributed to the change of the pH of the medium and not to a potential drug-excipient interaction (further investigations are needed to explain the nature of this change, as shifts in the pH of the media by the non-ionic HPMC are not expected).

Weak bases: For the majority of cases, significant reduction is observed in weak basic compound solubility at 24 hours by HPMC presence (-50% < REs < -20% for all the studied HPMC brands), especially in acidic conditions (**Figures 3.2 and 3.3**). The impact of pH on the apparent solubility of weak bases cannot be evaluated due to *in situ* salt formation between the drugs and counterions of the medium [60] (**Figure 3.4**), as explained in Chapter 2. The reduction in drug solubility in HPMC presence at

24 hours can be attributed to the slower drug dissolution/solubilization in excipient presence compared to absence. Significant increase in drug apparent solubility was observed for DPL in phosphate buffer pH 6.8 (38% < REs < 58%) and ITZ in FaSSIF-V2 (25% < REs < 61%) in presence of all the studied HPMC brands. Solubility data of DPL at 0.5, 4 and 24 hours in absence and presence of HPMC in phosphate buffer pH 6.8 and FaSSIF-V2 are presented in **Figure 3.6**. In phosphate buffer pH 6.8, increased DPL solubility in presence of HPMC is observed even at early time points (0.5 and 4 hours) and can be attributed to intermolecular interactions between the amine group of DPL and the hydroxyl group of HPMC which improve drug solubilization [61]. Presence of HPMC did not affected the DPL solubility in FaSSIF-V2 potentially due to the enhanced drug solubilization by the bile salts. ITZ forms a supersaturated solution in FaSSIF-V2 due to the micellar solubilization effect of bile salts and slowly precipitates with time [62]. The increase in ITZ apparent solubility in HPMC presence in FaSSIF-V2 can be attributed to the inhibition of drug precipitation by HPMC due to potential interaction of the neutral amine group of ITZ with the hydroxyl groups of HPMC.

The solubility data showed increased variability in the cases where HPMC presence significantly affected drug solubility at 24 hours (MTF: CV% > 40%, PRC or highly ionized poorly soluble drugs: 10% < CV% < 30%). As working with physical mixtures may yield high standard deviations due to the heterogeneous dispersion of the constituents [63, 64], the increased variability can be attributed to the heterogeneous saturation of powder surface with excipient particles.

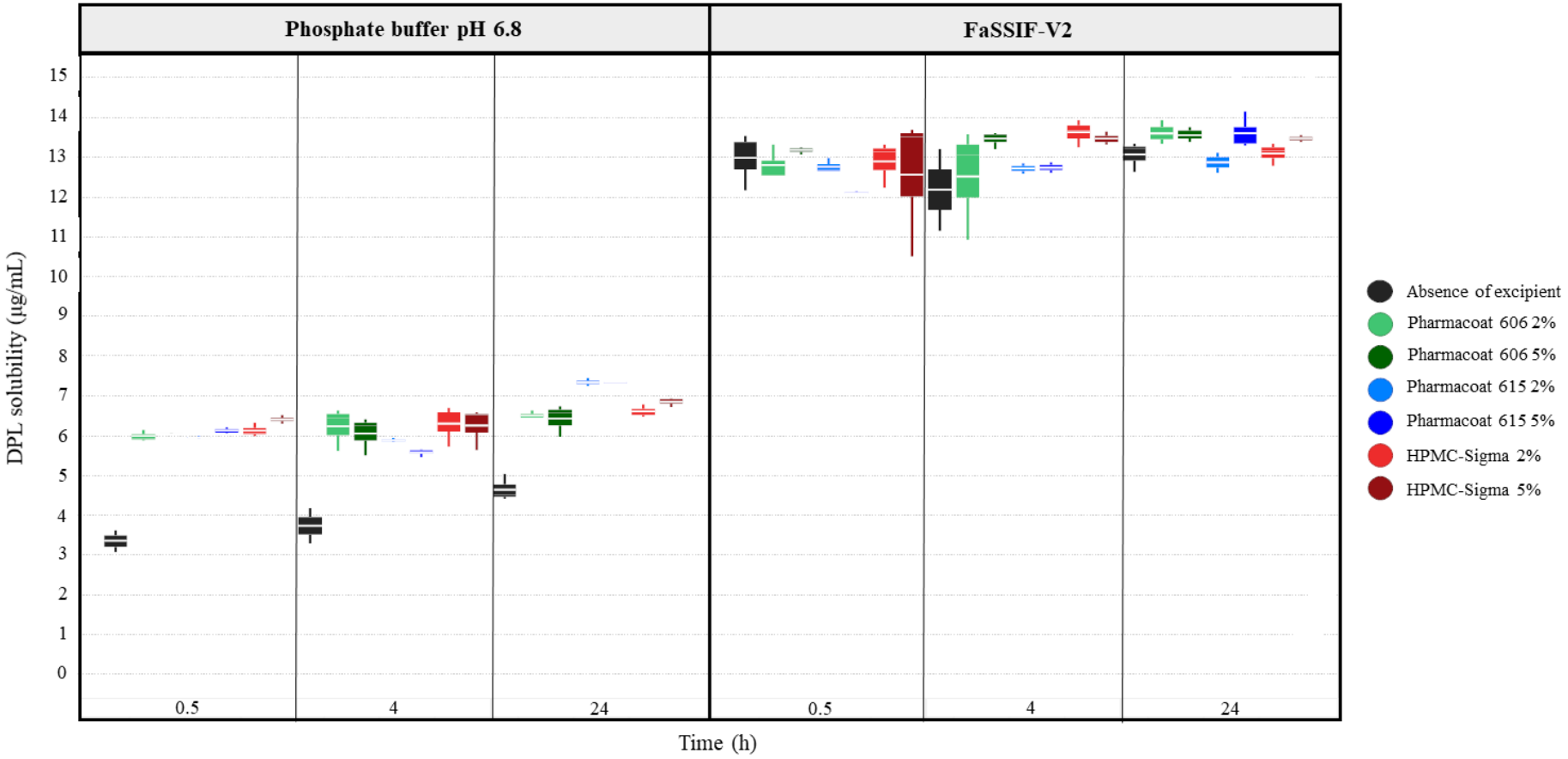


Figure 3.6: Box plots of DPL solubility (µg/mL) in absence (black colour) and presence (i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour) and iii. HPMC-Sigma (red colour)) in phosphate buffer pH 6.8 and FaSSIF-V2. Light and dark colours correspond to low and high excipient level, respectively. (Mean, n = 3)

3.3.2.2. Impact of excipients on drug apparent solubility based on drug physicochemical properties

The effects of the studied HPMC brands on the solubility of neutral drugs, weak acids and weak bases at 24 hours as a function of drug ionization and drug lipophilicity in compendial and biorelevant media are presented in **Figure 3.7**.

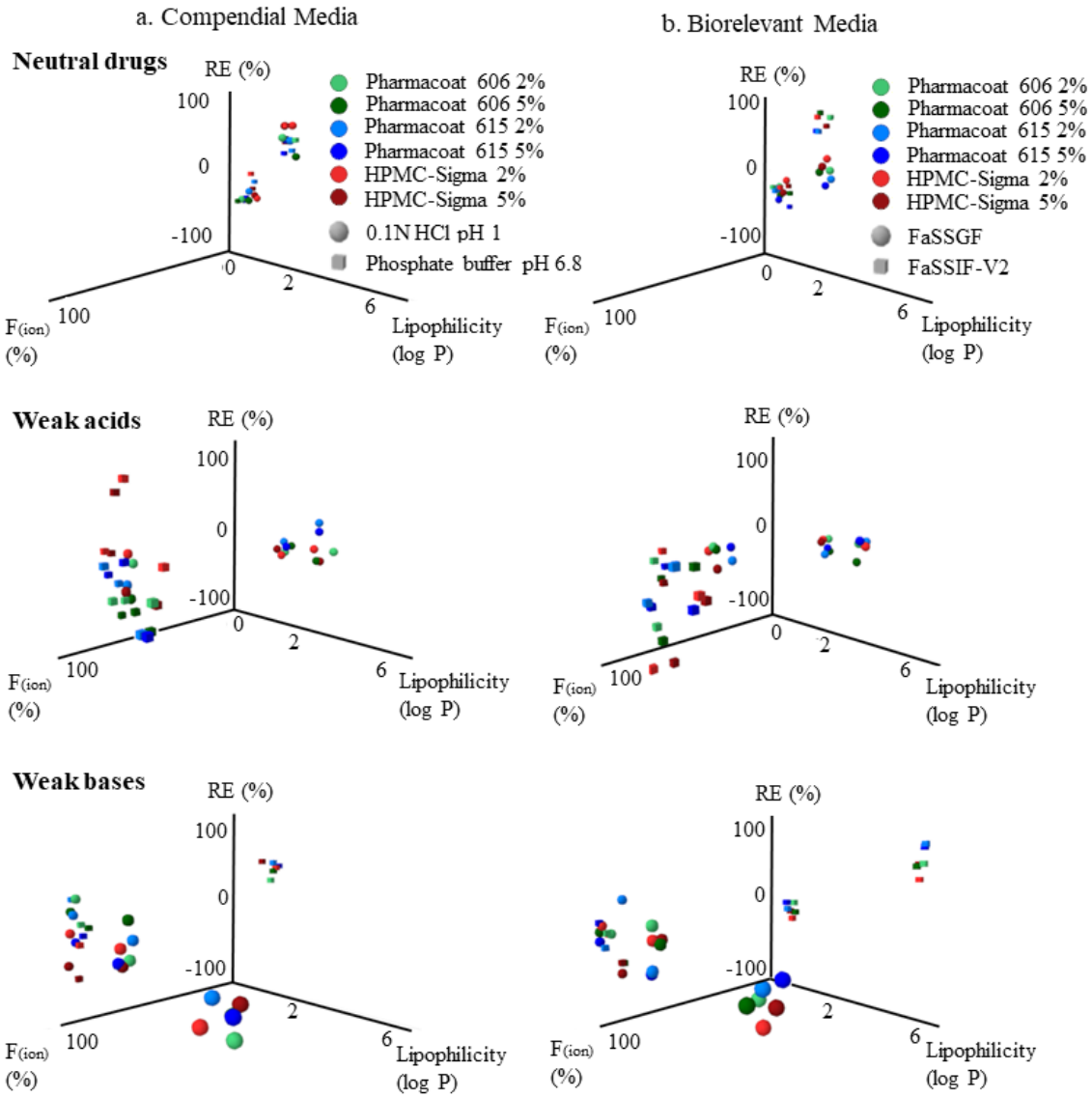


Figure 3.7: Relative effects (%) of the studied HPMC brands on drug solubility at 24 hours as a function of drug ionization (%) and drug lipophilicity (log P) in a. compendial and b. biorelevant media. The excipients brands are shown as: i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour), iii. HPMC-Sigma (red colour). Light and dark colours correspond to low and high excipient levels, respectively. Media representing gastric and intestinal conditions are presented as: i. acidic media (circles) and ii. basic media (squares).

For neutral drugs, the different effects of the HPMC brands on drug solubility at 24 hours (decrease and increase for the solubility values of PRC and CBZ, respectively) are attributed to the differences in drug lipophilicity between the two compounds (**Table 3.1**). For weak acids and weak bases, significant decrease in drug apparent solubility was observed in media (compendial or biorelevant) where drugs are highly ionized (excluding the cases of increased drug solubility attributed to the change of the pH of the medium). A trend between the impact of excipients on drug solubility at 24 hours and drug lipophilicity was found for weak bases in biorelevant media where drugs are unionized, as increased drug solubility was observed in HPMC presence for highly lipophilic drugs. The decrease in drug apparent solubility by HPMC presence was more pronounced with increasing level of drug ionization and/or decreasing drug lipophilicity (**Figure 3.7**) which can be explained by the presence of an increased number of excipient molecules on the powder surface [54, 65] (as explained in Chapter 2). Reduced drug mobility and slower drug diffusion have been reported for charged molecules due to interactions with the polymeric chains of HPMC [55] and may also have contributed to the decrease in the solubility of ionized molecules at 24 hours by HPMC. The classification gradient map depicting the effects of the studied HPMC brands on the 24 hour drug solubility as a function of decreasing drug aqueous solubility in compendial and biorelevant media is presented in **Figure 3.8**. The map confirms that the decrease in drug apparent solubility in presence of HPMC was more pronounced for highly soluble drugs which are inherently less lipophilic while for poorly soluble drugs, the reduction in drug solubility at 24 hours was more pronounced in media where drugs were highly ionized.

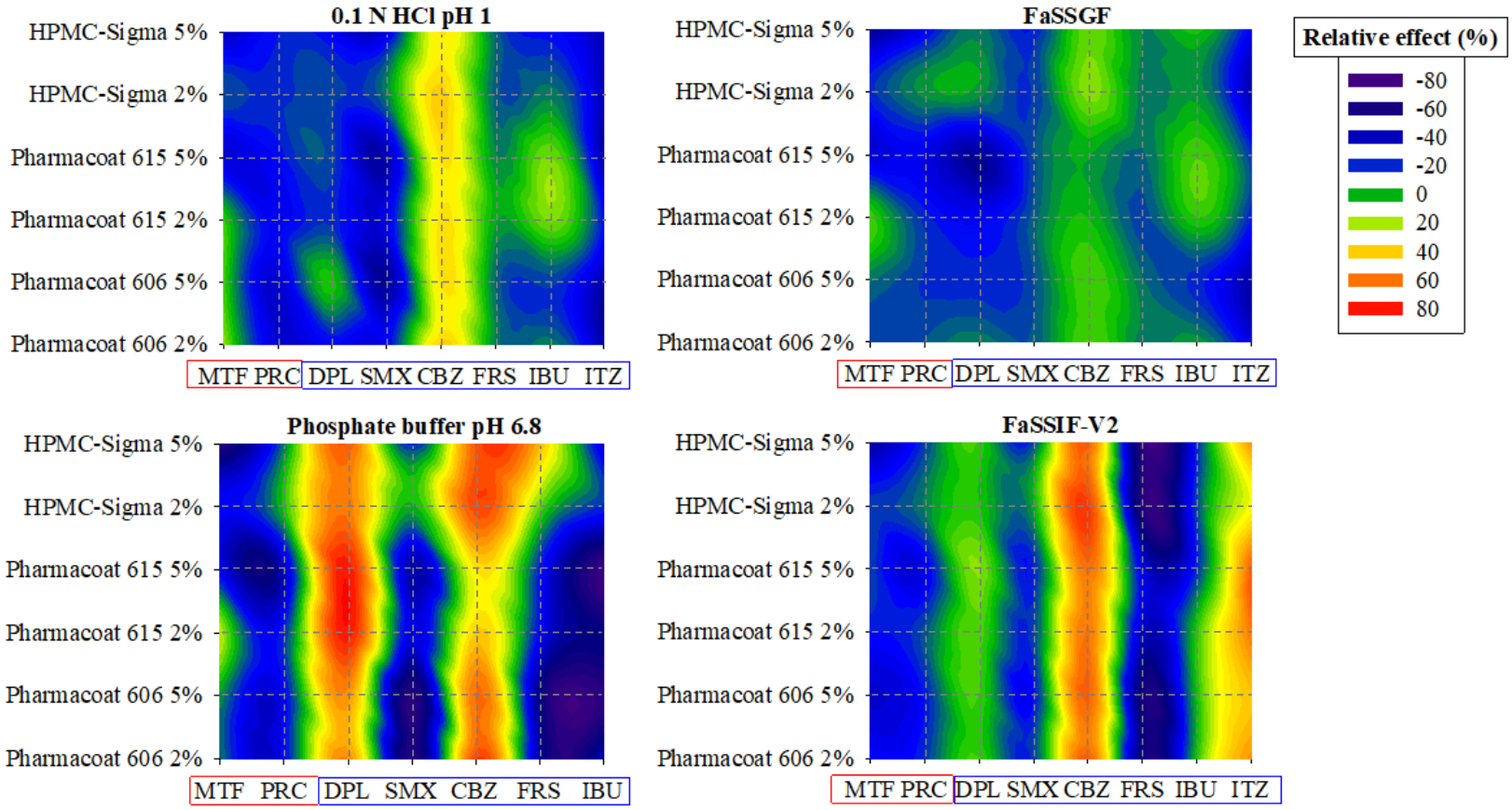


Figure 3.8: Classification gradient maps of the relative effects of the HPMC brands on the solubility of highly and poorly soluble compounds at 24 hours. Y-axes are set in an increasing excipient viscosity type and excipient level order. The x-axes are set in a decreasing drug aqueous solubility order (red colours for highly soluble and blue colours for poorly soluble drugs).

3.3.2.3. Impact of excipients on drug apparent solubility based on excipient properties

The effects of the studied HPMC brands on drug solubility as a function of drug ionization and time are presented in **Figure 3.9** (solubility data of CBZ in compendial and biorelevant media and of DPL in phosphate buffer pH 6.8 were not included in this visualization, as significant increase in drug solubility was observed).

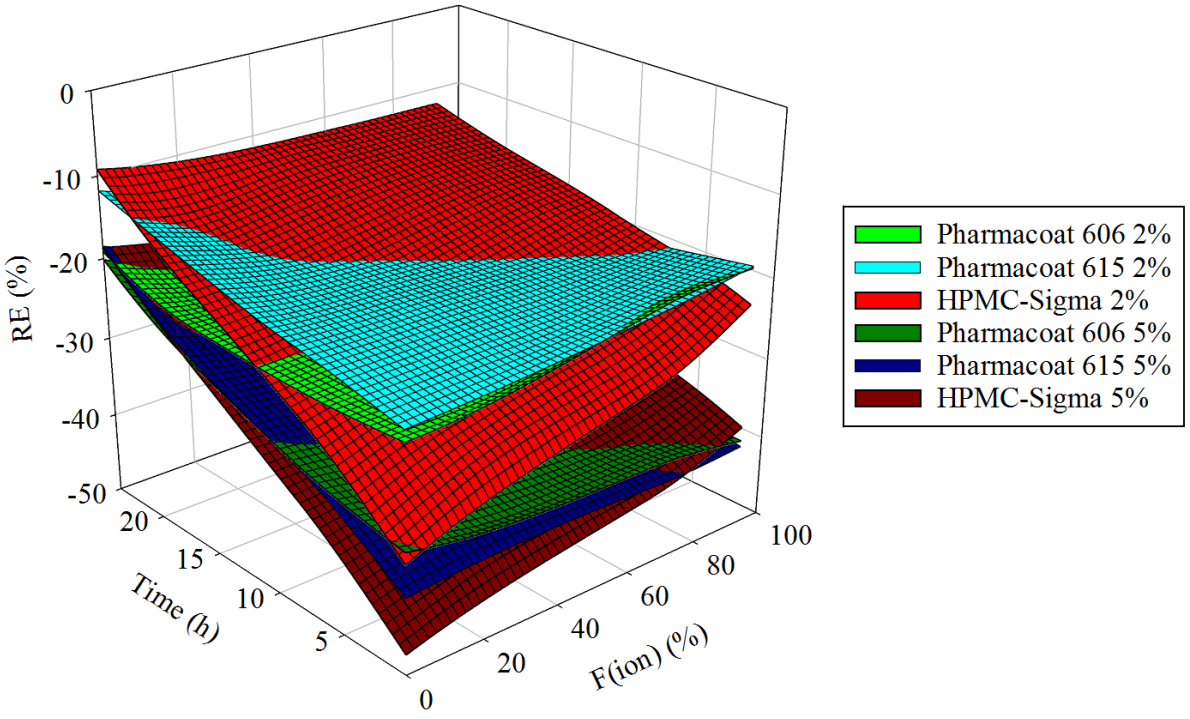


Figure 3.9: Relative effects of i. Pharmacoat 606 (green colour), ii. Pharmacoat 615 (blue colour) and iii. HPMC-Sigma (red colour) on drug apparent solubility as a function of drug ionization (%) and time (h). Light and dark colours correspond to low and high excipient level, respectively.

The decrease in drug apparent solubility by HPMC presence was more pronounced at early time points. When HPMC is used at low levels (< 10% w/w) in tablet formulations, a heterogeneous viscous HPMC layer is formed initially and cannot be maintained due to water penetration [17]. Therefore, the higher reduction in drug solubility at early compared to late time points may be explained by the disruption of the gel layer by water molecules. The high viscosity brand (HPMC-Sigma) resulted in higher reduction in drug solubility at early time points compared to the low viscosity

brands (Pharmacoat 606, Pharmacoat 615) which can be explained by the formation of a stronger gel layer by the high HPMC viscosity types compared to the low ones [9, 11, 12]. Increasing the level of all the studied HPMC brands resulted in higher reduction in drug apparent solubility compared to the low excipient level, as the increased number of chain entanglements, when increasing excipient level, leads to the formation of strong gel layer [14] which further delays drug dissolution and/or drug solubilization.

3.3.3. Multivariate Data Analysis

The standardized coefficients of the variables in compendial and biorelevant media are presented in **Figure 3.10**. The two models showed a good predictive power and fit (compendial media: $Q^2 = 0.7$ and $R^2 = 0.7$, biorelevant media: $Q^2 = 0.6$ and $R^2 = 0.6$). The statistical analysis reveals that the impact of HPMC on drug apparent solubility strongly depends on the physicochemical properties of the studied brands. Amine group (compendial media: positive effect, VIP = 3.2; biorelevant media: positive effect, VIP = 2.9) was a significant variable in both models. The variable amine group term indicates that pronounced increase in drug solubility at 24 hours in HPMC presence is expected for drugs containing a neutral amine group due to a potential drug-HPMC interaction which enhances drug solubilization. Pronounced reduction in drug apparent solubility is anticipated for highly ionized drugs, potentially due to the slower drug mobility and diffusivity by the presence of the viscous HPMC layer [55] as indicating by the significance of drug ionization (compendial media: negative effect, VIP = 2.2; biorelevant media: negative effect, VIP = 2.3) in both models. In biorelevant media, drug lipophilicity (positive effect, VIP = 1.3) and drug solubility (negative effect, VIP = 1.2) were also significant variables in the statistical models. Both variables indicate that pronounced reduction is expected for highly soluble/less lipophilic drugs as the enhanced drug solubilization caused by the presence of bile salts can result in saturation of the powder surface by HPMC particles. The statistical analysis demonstrates that, when HPMC is used as a binder, excipient variability and variation are not significant parameters for the impact of HPMC on drug apparent solubility.

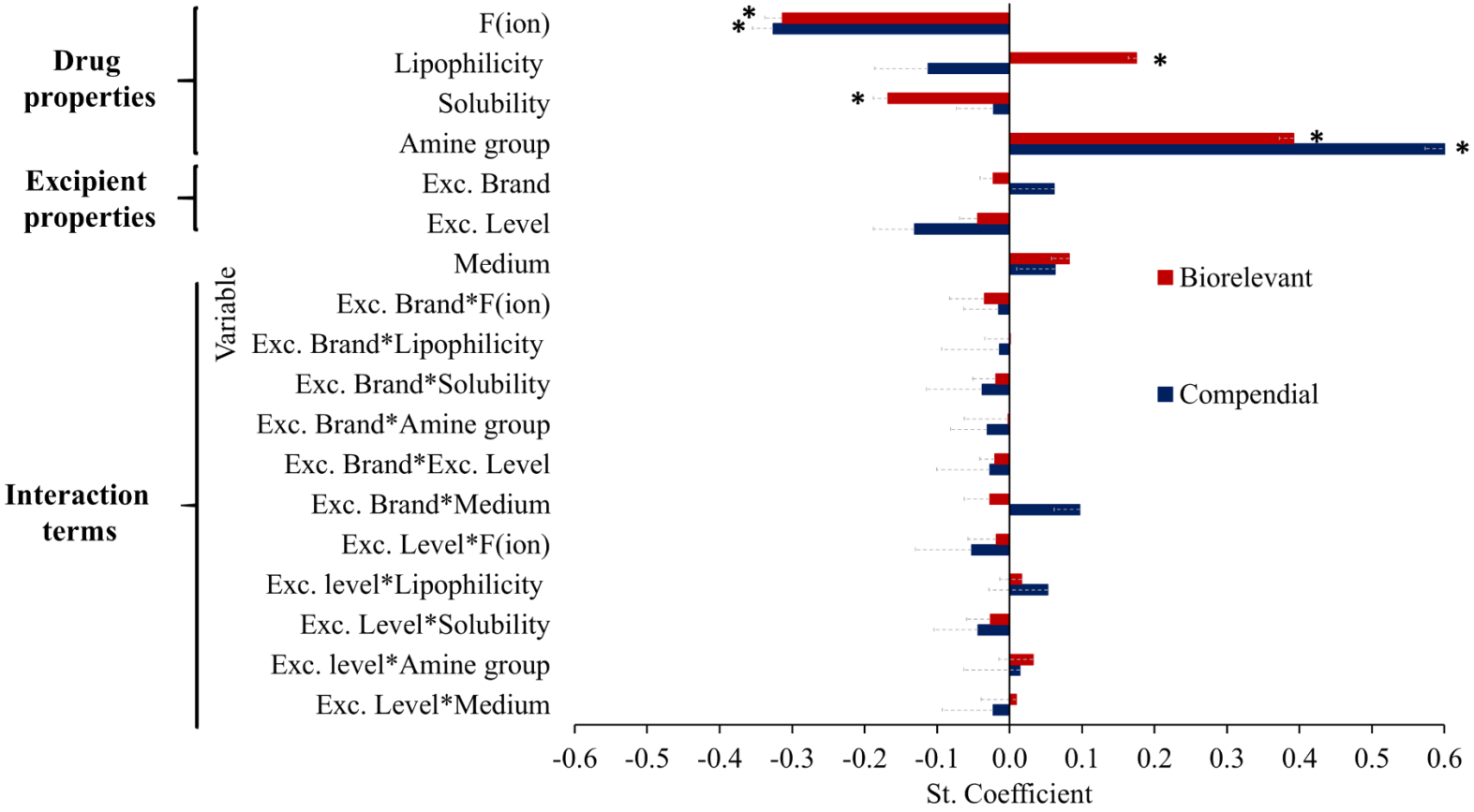


Figure 3.10: Standardized coefficients of the studied variables (and interaction terms) in compendial (blue colour) and biorelevant (red colour) media. * denotes coefficients of VIP > 1. * denotes coefficients of 0.8 < VIP < 1. (Mean, - SE)

3.3.4. Road map of excipient effects on drug apparent solubility

The road map categorizing the excipient REs on drug solubility at 24 hours according to excipient (HPMC) and drug properties is presented in **Figure 3.11** (cases where increased drug solubility was caused by a potential shift in the pH of the medium were not considered).

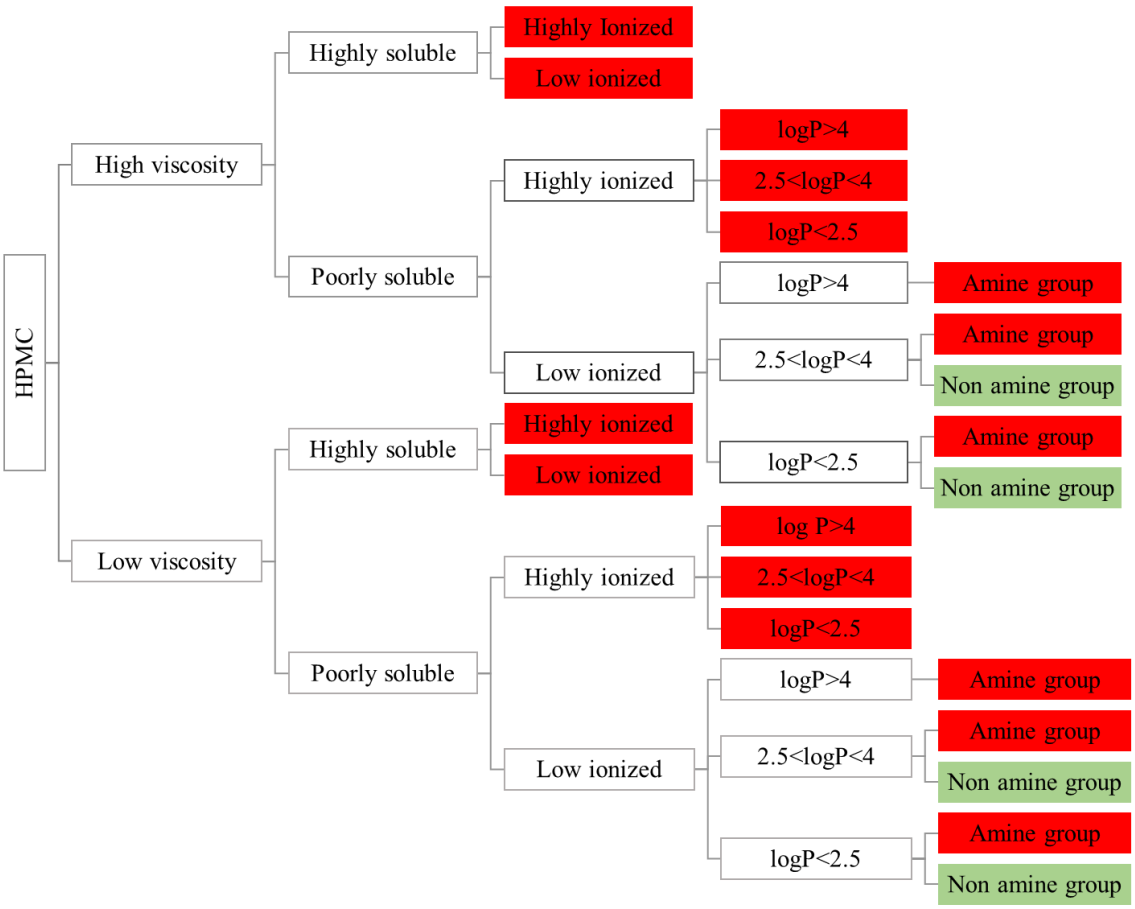


Figure 3.11: Road map of the effects of the studied excipients (low viscosity: Pharmacoat 606, Pharmacoat 615, high viscosity: HPMC-Sigma) on drug solubility at 24 hours. Red boxes and green boxes indicate significant and insignificant changes in drug solubility by excipient presence, respectively.

The impact of HPMC on drug apparent solubility depends on the physicochemical properties of the studied compounds. Significant changes (decrease) in drug solubility at 24 hours by HPMC brands of different viscosity type are anticipated for highly soluble drugs, irrespective of drug ionization state (low or highly ionized). For poorly soluble drugs, the impact of the studied HPMC brands on drug apparent solubility

depends on the drug ionization state, as significant decrease in drug solubility at 24 hours is expected when poorly soluble drugs are highly ionized (irrespective of drug lipophilicity). For poorly soluble/low ionized, HPMC is not found to affect drug solubility, apart from drugs containing a neutral amine group and for which presence of HPMC may result in significant increase in drug apparent solubility. The generated roadmap reveals that presence of HPMC may be challenging for oral drug performance, as differences in drug apparent solubility caused by the excipient may complicate oral drug absorption and bioavailability.

3.4. Conclusions

Excipient presence, variability and variation can affect product performance and present challenges for oral drug bioavailability. HPMC is a commonly used binder in immediate release formulations but can compromise drug dissolution as it forms a viscous layer around particles. In this work, the impact of HPMC viscosity type on drug apparent solubility was assessed in a biopharmaceutical perspective. Solubility studies showed that presence of HPMC can significantly change drug solubility at 24 hours, but its magnitude depends on drug physicochemical properties. Significant reduction in the apparent solubility of highly soluble or highly ionized drugs was observed potentially due to the formation of a viscous layer by HPMC. For poorly soluble drugs containing a neutral amine group, increase in drug apparent solubility was observed in HPMC presence attributed to the enhanced drug solubilization by the polymeric HPMC chains. Increasing HPMC viscosity and/or level resulted in pronounced decrease in drug solubility especially at early time points, as at the studied excipient levels, the formation of a viscous layer is disrupted by water penetration. The use of multivariate data analysis and the construction of roadmaps identified the cases where HPMC presence may be challenging for oral drug performance.

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Chapter 3 Commentary

Hypromellose (HPMC) is a commonly used binder or release controlling agent, when used in low and high levels, respectively in oral solid dosage forms. In this chapter, the impact of HPMC variability and variation on drug apparent solubility in a biopharmaceutical perspective was investigated by selecting three brands of HPMC of different viscosity type (Pharmacoat 606, Pharmacoat 615, HPMC-Sigma) in two different excipient levels. Compendial and biorelevant media were used to reflect the gastrointestinal conditions. For the majority of compounds, presence of HPMC decreased drug solubility at 24 hours and was attributed to a drug shielding effect by the excipient or the formation of viscous layer. The reduction in drug apparent solubility by HPMC was more pronounced for highly ionized and/or highly soluble less lipophilic drugs, due to the fast saturation of the powder surface by excipient particles. The reduction in drug solubility by HPMC was more pronounced at early time points, as at the studied excipient amounts, the initial HPMC viscous layer cannot be maintained due to water penetration. Increasing HPMC viscosity or level resulted in higher reduction in drug apparent solubility, especially at early time points, as a result of the formation of thicker viscous layer delaying drug dissolution from the powder surface. Presence of HPMC increased the apparent solubility of poorly soluble drugs containing a neutral amine group, as a result of enhanced drug solubilization or a drug-excipient interaction delaying drug precipitation. The statistical analysis and the contruction of the roadmap revealed that, when HPMC is used as a binder, drug physicochemical properties, rather than excipient properties, are the critical factors affecting the impact of HPMC on drug apparent solubility.

Chapter 4 Preface

Pharmaceutical Quality by Design (QbD) requires the sound understanding and control of excipient variability to assure product safety and efficacy. Superdisintegrants are polymeric excipients which provide fast tablet disintegration and improve drug dissolution in immediate release formulations. Sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CPV) are the most frequently used superdisintegrants due to their ability to absorb water through swelling (SSG, CCS) or shape recovery (CPV) within seconds. The critical material properties and the biopharmaceutical factors affecting the impact of superdisintegrants on oral product performance are not well documented. Superdisintegrant interchangeability is also questionable as changes in tablet disintegrations and/or drug dissolution have been reported despite the use of structurally similar excipients (SSG, CCS). It follows that designing *in vitro* biorelevant methods to gain an indepth knowledge of the superdisintegrant effects on oral drug performance is crucial and would pave the way towards excipient implementation in the QbD approach. The aim of this chapter is to investigate the impact of superdisintegrant presence and variability on drug apparent solubility in a biopharmaceutical perspective. The use of multivariate data analysis and the construction of roadmaps will allow the identification of cases where superdisintegrants can be challenging for oral drug absorption. The results from this study, in conjuction with data presented in Chapter 2 and 3, form a broad data set where the biopharmaceutical implications of excipient presence and variability are systematically reviewed.

Chapter 4. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties. Case study: Superdisintegrants

Abstract

The presence of different excipient types/brands in solid oral dosage forms may affect product performance and drug bioavailability. Understanding the biopharmaceutical risks of excipients on oral drug performance is crucial for the development of products with robust *in vivo* performance. The current study investigated the impact of superdisintegrants (sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CPV)) on the apparent solubility of drugs with different physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility). Compendial and biorelevant media were used to assess the impact of gastrointestinal (GI) conditions on the effects of excipients on drug apparent solubility. For the majority of compounds, changes in drug apparent solubility in superdisintegrant presence were not observed, apart from the cases of highly ionized drugs (significant reduction in drug solubility) and/or drugs that aggregate/precipitate in solution (significant increase in drug solubility). Excipient variability did not greatly affect the impact of excipients on drug solubility. The use of multivariate data analysis identified the biopharmaceutical factors affecting excipient performance. Based on drug solubility data, the construction of roadmaps revealed that superdisintegrants may be of low risk for the impact of excipients on oral drug performance (superdisintegrant effectiveness in oral solid dosage forms could still be of high risk for oral bioavailability).

Keywords: excipient variability, sodium starch glycolate, croscarmellose sodium, crospovidone, drug solubility

4.1. Introduction

Introduction of the Quality by Design (QbD) initiative in pharmaceutical development requires the scientific understanding of the components and processes affecting final product qualities [1]. The critical role of excipients in product performance and oral bioavailability is highlighted as presence of excipients in oral formulations may affect the biopharmaceutical profile of drugs with potential implications on drug absorption [2, 3]. Excipient variability or variation and the use of different excipients with the same intended functionality may further complicate the impact of excipients on oral drug bioavailability [4]. The heterogeneous composition of the gastrointestinal tract may as well modify the properties and functionality of excipients and presents an additional challenge to assess the impact of excipients on product performance [4].

Superdisintegrants are commonly used in immediate release formulations as they promote fast tablet disintegration and improve drug dissolution. Sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CPV) are three commonly used crosslinked superdisintegrants due to their ability to absorb water and/or swell in low concentrations (typically 2% - 8% for SSG [5], 0.5% - 5% for CCS [6] and 2% - 5% w/w for CPV [7] in tablet formulations [8]. SSG (**Figure 4.1a**) and CCS (**Figure 4.1b**) are sodium salts and their ionization state differs between acidic (neutral form) and basic (ionized form) conditions, while CPV is a non-ionic polymer (**Figure 4.1c**). Swelling and shape recovery are the main suggested mechanisms by which superdisintegrants induce tablet disintegration. Swelling refers to the volumetric expansion of excipient particles due to water absorption while shape recovery refers to excipient deformation upon contact with water [9]. Real-time magnetic resonance imaging identified that SSG and CCS act through swelling while CPV through shape recovery [10]. The limited knowledge on superdisintegrant molecular structure, interplay with other pharmaceutical components and performance in the gastrointestinal conditions is challenging for manufacturers [9]. Superdisintegrant interchangeability could be questioned without appropriate identification of the biopharmaceutical consequences of their use.

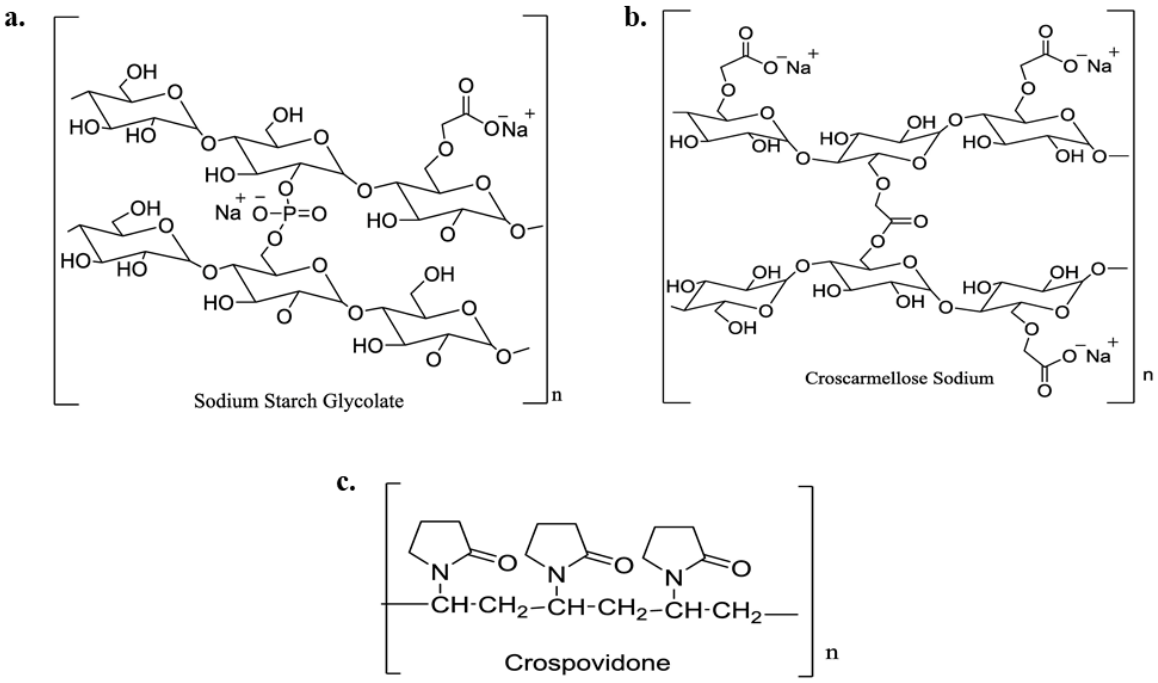


Figure 4.1: Chemical structure of a. Sodium Starch Glycolate, b. Croscarmellose Sodium and c. Crospovidone (ChemDraw Professional 15).

Molecular properties (composition), particle properties (particle size distribution (PSD)) and level have been identified as the critical material attributes affecting excipient performance (for CPV, molecular properties were not critical) [4]. For SSG and CCS, the degree of substitution and degree of crosslinking are critical functional properties. The degree of substitution (presence of the carboxymethyl group) increases polymer hydrophilicity and swelling [11]. The degree of crosslinking reduces the excipient soluble content which can increase the viscosity of the surrounding medium and compromise tablet disintegration [4]. PSD affects the swelling capacity of SSG and CCS, as larger particles swell more extensively compared to smaller particles [11]. For CPV which exhibits a more porous structure, PSD relates to water uptake as the higher porosity of larger particles results in faster water absorption and tablet disintegration [12]. Finally, increasing excipient level in tablet formulations leads to faster water uptake and tablet disintegration, but care should be taken when using gelling superdisintegrants as high excipient levels may result in the formation of viscous layers around drug particles [13].

The biopharmaceutical implications of superdisintegrants are not fully understood. The pH of the medium affects the performance of SSG and CCS due to the ionization

pattern of the excipients. The swelling ability of the neutral form is reduced due to its low hydration capacity compared to the ionized form [8]. The performance of superdisintegrants can also relate to drug physicochemical properties. Electrostatic interactions between cationic drugs and the carboxyl group of SSG and CCS are known to affect the % of drug recovery during routine drug analysis [14, 15] or delay drug release from tablet formulations [16]. Drug-excipient interactions are affected by the presence of salts, as high salt concentrations supress the binding of drugs in the hydrogels [17]. Adsorption of lipophilic molecules to CPV through hydrophobic interactions has been reported [17] that could also affect drug release from pharmaceutical formulations.

The aim of this study was to investigate the biopharmaceutical implications and criticality of superdisintegrant variability and variation on drug apparent solubility. The impact of excipient variability on drug apparent solubility was studied by selecting three SSG brands of different viscosity type and two CCS and CPV brands of different PSD. Two excipient levels (low: 2% w/w, high: 5% w/w) were used to assess the impact of excipient variation on drug apparent solubility. The biopharmaceutical implications of superdisintegrant variability were evaluated by choosing compounds with different physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and media (compendial and biorelevant) representing the gastric and intestinal compartments. The significance of drug properties, excipient presence and medium characteristics on the effects of superdisintegrants on drug apparent solubility were investigated with the use of multivariate data analysis (Partial Least Squares (PLS)) and the design of roadmaps.

4.2. Materials and Methods

4.2.1. Materials

APIs: Sulfamethoxazole and paracetamol were obtained from Fisher Scientific (UK). Furosemide, itraconazole and dipyridamole were obtained from VWR (UK). Ibuprofen, carbamazepine and metformin were obtained from Fagron (UK). Excipients: Glycolys LV and Glycolys (Roquette, France), Explotab CLV (JRS Pharma, USA), Kollidon CL-F and Kollidon CL (BASF-SE, Germany), AcDiSol (FMC, USA) and Primellose (DFE Pharma, Germany) were obtained from the specified sources. Chemicals: Acetic acid (>99.7%), hydrochloric acid 36.5–38%,

HPLC grade methanol, HPLC grade acetonitrile, dichloromethane, pepsin (from porcine) were obtained from Sigma-Aldrich (UK). Maleic acid, sodium chloride, sodium hydroxide, potassium phosphate monobasic, sodium dihydrogen orthophosphate dihydrate, disodium hydrogen orthophosphate dihydrate, potassium dihydrogen orthophosphate, anhydrous sodium sulfate, HPLC grade trifluoroacetic acid were obtained from Fisher Scientific (UK). Sodium taurocholate (Prodotti Chimici Alimentari S.P.A., Italy), egg lecithin – Lipoid EPCS (Lipoid GmbH, Germany), were obtained from the sources specified. Water was ultra-pure (Milli-Q) laboratory grade. Filters: Whatman® 13 mm cellulose nitrate filters 0.45 μm pore size and polytetrafluoroethylene (PTFE) 13 mm filter 0.45 μm pore size were purchased from Fisher Scientific (UK).

4.2.2. Instrumentation

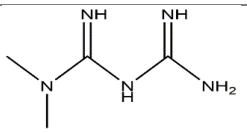
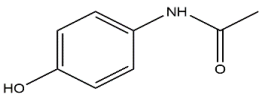
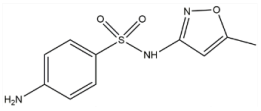
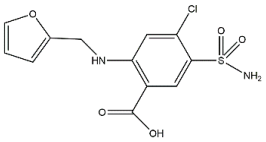
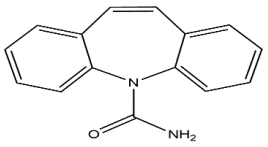
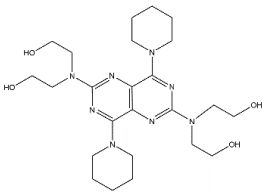
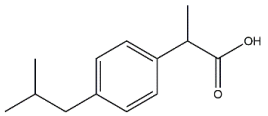
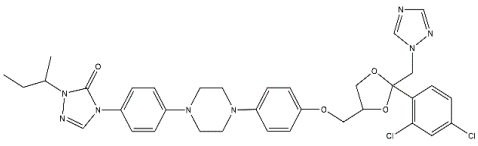
Fisherbrand waterbath (Fisher Scientific, UK), Sartorius BP 210 D balance (Sartorius Ltd, UK), Buchi R114 Rotavapor (Buchi, Switzerland), Mettler Toledo SevenCompact S210 pH meter (Mettler Toledo, Switzerland), Vortex-Genie 2 vortex mixer (Scientific Industries Inc, USA), Brookfield HA-RVIII viscometer (Brookfield Ametek, USA), Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A), autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector (G1329A) and Chemstation software (Agilent Technologies, USA).

4.2.3. Methods

4.2.3.1. Compounds selected for solubility experiments

The compounds used for the solubility experiments, their physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility) and their structure are presented in **Table 4.1**.

Table 4.1: Physicochemical properties and structure of the compounds used for the solubility experiments. (ChemDraw Professional 15)

Drug	Ionization	Lipophilicity (log P)*	Solubility	Chemical Structure
Metformin (MTF)	Weak base (pKa=2.8) [18]	-0.5[a]	High [18]	
Paracetamol (PRC)	Neutral (pKa=9.38) [19]	0.46[a]	High [19]	
Sulfamethoxazole (SMX)	Weak acid (pKa_1=1.7, pKa_2=5.6) [20]	0.89[a]	Low [21]	
Furosemide (FRS)	Weak acid (pKa=3.8) [22]	2.29 [22]	Low [22]	
Carbamazepine (CBZ)	Neutral (pKa=15)[a]	2.45[a]	Low[a]	
Dipyridamole (DPL)	Weak base (pKa=6.2) [23]	2.74 [24]	Low [25]	
Ibuprofen (IBU)	Weak acid (pKa=4.5) [26]	3.97[a]	Low [26]	
Itraconazole (ITZ)	Weak base (pKa=4.5) [27]	5.66[a]	Low [28]	

*Experimental values

[a]Source: DrugBank

4.2.3.2. Media prepared for solubility experiments

Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to the method described in the United States Pharmacopeia [29]. Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF-V2) were prepared as per literature references [30].

4.2.3.3. Design of experiments (DoE) used for solubility experiments

A full-factorial Design of Experiments (DoE) was performed to determine the number of necessary experiments using StatGraphics Centurion XVII (Statpoint Technologies Inc, USA). As drug solubility will differ according to the composition of the studied media (pH, presence of bile salts), two models for the DoE were constructed to discriminate between the effects of excipients on drug apparent solubility in compendial (Model 1) and biorelevant conditions (Model 2). The examined factors were: i. compound (**Table 4.1**), ii. excipient brand (SSG: Glycolys LV, Explotab CLV, Glycolys, CCS: AcDiSol, Primellose, CPV: Kollidon CL-F, Kollidon CL), iii. excipient level (low, high), iv. medium (gastric, intestinal). The impact of each excipient on drug apparent solubility [expressed as the relative increase or decrease in drug solubility in presence compared to absence of excipient (section 4.2.3.6)] was set as the response. A total of 224x3 experiments was determined for each model. 16x3 additional experiments in triplicate for each model were conducted to determine drug apparent solubility in the corresponding media in the absence of excipient. These experiments were not included in the DoE as drug solubility in excipient absence was measured only for the calculation of relative excipient effects on drug solubility.

4.2.3.4. Characterization of superdisintegrants

4.2.3.4.1. Viscosity measurements

Samples of each superdisintegrant were prepared as 3% w/v dispersions in water. 0.5 mL of each sample was loaded into the cup of a rotational viscometer. The viscosity of each dispersion was measured every 10 minutes for an hour at 25°C using a CPA-40z spindle rotated at a speed of 120 rpm [31]. All experiments were performed in triplicate.

4.2.3.4.2. Particle Size Distribution

The PSD of the studied CCS and CPV brands was measured using laser diffraction (dry dispersion) and the cumulative undersized particle parameters d_{10} (μm), d_{50} (μm) and d_{90} (μm) were calculated (data kindly provided by AstraZeneca).

4.2.3.5. Solubility studies

Drug solubility studies in the absence and presence of excipient were performed in triplicate using the shake-flask method [32]. Drug excess and 2% w/w or 5% w/w of each excipient were weighed and placed in centrifuge tubes. The amount of excipient was determined as follows: i. for poorly soluble drugs, considering an average of 500 mg tablet weight [33] (which resulted in 9% w/w (low level) and 20% w/w (high level) of excipient in the total volume of the physical mixture) and ii. for highly soluble drugs, according to the amount of drug excess and the % w/w of excipient in the total volume of the physical mixture based on point (i). The physical mixtures were vortexed for 3 minutes. 5 mL of each medium were added in the tubes and the samples were placed in a shaking water bath (37 °C, 200 strokes per minute (spm)). At 0.5, 4 and 24 hours (for PRC, SMX, CBZ, DPL, IBU) and at 24 hours (for MTF, FRS, ITZ), 500 μL were sampled and filtered through PTFE filters (or cellulose nitrate filters for the cases of IBU and CBZ). Filter adsorption studies were prior performed in triplicate for each drug. No adsorption issues onto the filters used were observed for the studied drugs. Filtered samples were further diluted (if needed) with the corresponding medium and analysed by HPLC (**Table 4.2**). Analytical HPLC procedures for drug quantification in the samples were modifications of already published methods. Drug quantification was made based on calibration curves. Standards were formulated from concentrated stock solution consisting of drug dissolved in MeOH. As changes in the pH of solutions by presence of dissolved drug [25] may affect drug solubility, the pH of samples after the completion of each experiment was measured. Drug apparent solubility was calculated based on the sample drug concentration measured. Solubility values measured experimentally in excipient absence for neutral drugs, for weak acids in acidic media and for weak bases in basic media determined the intrinsic solubility values. Solubility values measured experimentally in excipient absence in basic media (for weak acids) and acidic media (for weak bases) determined drug solubility of the ionized molecules.

Table 4.2: HPLC methods used for drug quantification

	Column	Mobile Phase	Flow Rate (mL/min)	Temp (°C)	Inj. Vol. (µL)	Detection wavelength (nm)	R_t (min)	Concentration of stock solutions (mg/mL)	Calibration range in acidic media (µg/mL)	Calibration range in basic media (µg/mL)	Reference
MTF	Inertsil Phenyl (Metachem) 250x3mm - 5µm	MeOH/Phosphate buffer pH 7 (70:30)	1	20	20	236	8	2	10 - 200	10 - 200	[34]
PRC	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (20:80)	1	20	20	257	6	2	10 - 200	10 - 200	[35]
SMX	Polaris (Metachem) C18 250x4.6mm – 5µm	MeOH/Phosphate buffer pH 6.8 (20:80)	1	25	20	257	7	1	10 - 200	50 – 500	[36]
FRS	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/water with 0.1% formic acid (50:50)	1	25	50	232	4	1	2 – 20	10 - 200	[37]
CBZ	Spherisorb (Waters) C18 250x4.6mm - 5µm	MeOH/Water (60:40)	1	25	100	285	4	1	10 – 150	10 - 150	[38]
DPL	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/water with 0.1% TFA (30:70)	1	25	50	284	6	1	10 -200	Compendial 1 - 5 Biorelevant 2 - 10	[39]
IBU	Eclipse XDB-C18(Agilent) 250x4.6mm – 5µm	MeOH/water with 0.2% acetic acid (65:35)	1	25	100	233	6	1	5 – 40	10 - 200	[40]
ITZ*	XBridge Shield C18 150x4.6mm – 3.5µm	ACN/phosphate buffer pH 3 (60:40)	1	20	100	Emission: 252 Excitation: 360	8	0.1	Compendial 0.5 – 5 Biorelevant 0.1 - 10	0.015 – 0.06	[41]

*Quantification was made using HPLC-Fluorescence

4.2.3.6. Treatment of *in vitro* solubility data

The Relative Effect (RE) of each excipient on drug apparent solubility was calculated based on equation 4.1:

$$RE = \frac{(S-Sr)}{Sr}\ x\ 100 \qquad \text{(Equation 4.1)}$$

where S and Sr denote drug solubility in presence and absence (reference solubility) of excipient at 0.5, 4 and 24 hours. REs of excipients on drug apparent solubility > 25% or < -20% were considered as significant change in drug apparent solubility to assess excipient criticality (this range was selected as a similar range is set in order to assess differences in drug exposure after oral administration; i.e. in bioequivalence studies) [42].

Box plots depicting the impact of excipients on drug solubility at 24 hours for all the studied compounds or as a function of time (0.5, 4 and 24 hours) for CBZ were constructed using Spotfire 7.10.1 (TIBCO software Inc, USA). The classification gradient maps portraying the impact of the studied brands on drug apparent solubility as a function of drug aqueous solubility were generated using SigmaPlot 13.0 (Systat Software Inc, USA).

In cases where drug intrinsic solubility was not determined experimentally, the theoretical intrinsic solubility was calculated using the solubility-pH equations (Equations 4.2-4.5) [43]:

$$\log S = \log S_o + \log(10^{-pKa+pH} + 1) \qquad \text{for weak acids (Equation 4.2)}$$

$$\log S = \log S_o + \log(10^{pKa-pH} + 1) \qquad \text{for weak bases (Equation 4.3)}$$

$$\log S = \log S_o + \log(10^{+pKa_2+pKa_1-2pH} + 10^{pKa_2-pH} + 1) \qquad \text{for diprotic bases (Equation 4.4)}$$

$$\log S = \log S_o + \log(10^{+pKa_1-pH} + 10^{-pKa_2+pH} + 1) \qquad \text{for ampholytes (Equation 4.5)}$$

where S and S_o indicate drug solubility at the given pH and the intrinsic solubility, respectively. The final pH and experimental solubility values of the ionized drug in basic (for weak acids) or acidic media (for weak bases) were used for the calculation of the theoretical intrinsic solubility. Theoretical pH-solubility profiles in

the physiological pH range were constructed to assess if changes in the pH of the medium could justify differences in drug solubility by excipient presence. The final pH and intrinsic solubility values (experimental or theoretical) were used for the construction of the theoretical pH – solubility profiles in the physiological pH range based on Equations 4.2 -4.5.

4.2.3.7. Multivariate Data Analysis

Excipient REs on drug apparent solubility were correlated to drug physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility), excipient critical material attributes (viscosity for SSG, PSD for CCS and CPV, level) and medium characteristics (gastric, intestinal) by partial least squares (PLS) regression using the XLSTAT software (Microsoft, USA). Two models for the REs of excipients on drug solubility in compendial media (Model 1) and biorelevant media (Model 2) were constructed. The evaluated variables for both models were categorized according to their type as categorical (expressing a category or type) and numerical (measurements with numerical meaning). Categorical variables included i. drug solubility (poor, high), ii. amine group (absence, presence), iii. excipient brand (low and high PSD for CCS and CPV), iv. excipient level (low, high), v. medium (gastric, intestinal) while numerical parameters included i. % of drug ionized (F_{ion}; calculated based on the Henderson – Hasselbalch equation at the pH of each medium), ii. drug lipophilicity (log P), iii. excipient brand (viscosity in cP of dispersion after 1 hour for SSG). Excipient REs on drug solubility at 24 hours were used as the response. The selected interaction terms included each excipient property combined with each drug physicochemical property (drug ionization, drug lipophilicity, drug aqueous solubility) and medium characteristics (gastric, intestinal). Observation diagnostics were performed prior to model analysis to identify outliers in the data set. The distance of each observation to the model in the Y-plane (DmodY) tool based on PLS residuals was used. Plots of standardized DmodY vs each observation were generated and any observation exceeding the maximum tolerance volume in Y ($Dcrit_{(Y)}$) was considered an outlier [44, 45]. Exclusion of outliers was based on two criteria: i. deviating cases (positive REs) in solubility caused by a pH shift of the solution, ii. observations resulting in high variability (coefficient of variation (CV%) > 20%) within the triplicate samples (one value from the triplicate could be excluded as the outlier analysis could detect these values). PLS models generated with and without outlier

exclusion (data not shown) confirmed that outlier exclusion did not alter the interpretation of results but only enhanced the predictive ability of the regression model. The generated models were assessed in terms of goodness of fit (R^2) and goodness of prediction (Q^2). High values of R^2 and Q^2 with a difference not greater than 0.2 - 0.3 were indications of successful models [46]. The number of PLS components (lines on the X-space which best approximate and correlate with the Y-vector) was based on minimum predictive residual sum of squares (PRESS) [46]. From the available components the one at which Q2 reached its maximum value was selected [44]. Standardized coefficients were used to show the direction (positive or negative) and extent of each variable on the response. The significance of the selected variables was assessed by the variable influence on projection (VIP) value. VIP values > 0.8 were considered as moderately influential in the model while VIP values > 1 were considered the most influential in the model [46]. A 95 % confidence interval was used.

4.2.3.8. Roadmap Design

Roadmap designs for identifying potential biopharmaceutical risks of superdisintegrant variability on drug apparent solubility were constructed by combining the impact of excipients on drug solubility from the solubility studies to excipient (viscosity for SSG, PSD for CCS and CPV) and drug (drug ionization, drug lipophilicity, drug aqueous solubility) physicochemical properties. Drugs were categorized according to drug aqueous solubility and drug lipophilicity (**Table 4.1**) and drug ionization (low ionized: $F_{(ion)} < 50\%$, highly ionized: $F_{(ion)} > 50\%$). The risk assessment of the impact of excipients on drug apparent solubility was evaluated by setting reference range criteria of -20% - 25% [42] on the REs of excipient on drug solubility at 24 hours. REs of excipients on drug solubility outside these values (REs < -20% or REs > 25%) were considered critical for oral drug performance.

4.3. Results and Discussion

4.3.1. Characterization of superdisintegrants

The viscosity data of the studied excipient types and brands are presented in **Table 4.3**. The viscosity of a superdisintegrant dispersion with time relates to the degree of crosslinking [31]. The SSG dispersions exhibit higher viscosity values compared to the CCS or CPV dispersions indicating that the SSG brands contain higher soluble

material content compared to the CCS and CPV brands, which increases the viscosity of the dispersion over time [9]. The higher degree of crosslinking for Glycolys LV and Explotab CLV explains the lower viscosity of their aqueous dispersion compared to the dispersion of Glycolys, as fewer polymeric chains are able to dissolve in the surrounding medium. Differences in the viscosity of dispersions between the different brands of CCS and CPV are not revealed. Experimental data of PSD (kindly provided by AstraZeneca) for the studied CCS and CPV brands are summarized in **Table 4.4**. AcDiSol comprised of smaller particles compared to Primellose, therefore the CCS brands will be referred as CCS(L) (AcDiSol) and CCS(H) (Primellose) in the sections below. Differences in the PSD were also observed for the CPV brands, as the particle size of Kollidon CL-F was smaller compared to Kollidon-CL and therefore Kollidon CL-F and Kollidon-CL will be referred as CPV(L) and CPV(H), respectively in the sections below.

Table 4.3: Viscosity (cP) of the studied superdisintegrant brands (Mean ± SD)

Time (min)	**SSG**		**CCS**			**CPV**	
	Glycolys LV	Explotab CLV	Glycolys	CCS(L)	CCS(H)	CPV(L)	CPV(H)
10	9.7 (± 0.3)	11.7 (± 0.6)	18.6 (± 1.6)	8.2 (± 1.1)	9.1 (± 0.7)	1.6 (± 0.1)	2.4 (± 0.2)
20	9.9 (± 0.3)	11.9 (± 0.6)	19.1 (± 1.8)	7.6 (± 0.8)	8.8 (± 0.8)	1.5 (± 0.1)	2.0 (± 0.3)
30	10.1 (± 0.3)	12.1 (± 0.6)	19.6 (± 2.0)	7.5 (± 0.7)	8.4 (± 0.7)	1.5 (± 0.1)	1.9 (± 0.3)
40	10.3 (± 0.3)	12.3 (± 0.5)	19.9 (± 2.1)	7.5 (± 0.7)	8.0 (± 0.9)	1.5 (± 0.1)	1.7 (± 0.3)
50	10.5 (± 0.3)	12.4 (± 0.24)	20.3 (± 2.2)	7.5 (± 0.6)	8.2 (± 0.9)	1.5 (± 0.1)	1.6 (± 0.1)
60	10.6 (± 0.2)	12.7 (± 0.3)	20.6 (± 2.3)	7.5 (± 0.5)	7.6 (± 0.8)	1.5 (± 0.0)	1.6 (± 0.2)

Table 4.4: Particle size distribution of the studied CCS and CPV brands

Brand Name	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
CCS(L)	12.8	31.9	74.2
CCS(H)	21.8	52.2	109.8
CPV(L)	12.1	36.3	117.4
CPV(H)	15.9	77.6	234.3

4.3.2. Solubility studies

4.3.2.1. Impact of superdisintegrants on drug apparent solubility

The reference drug solubility values at 24 hours in compendial and biorelevant media are summarized in **Table 4.5**. From the studied compounds, only weak acid or weak bases showed a pH – dependent solubility, as expected (except from the case of MTF, as explained in Chapters 2 and 3). For neutral drugs or weak acids/weak bases in media where drugs are unionized, reference solubility values were higher in biorelevant compared to compendial media, due to the presence of solubilizing components [47]. For weak acids or weak bases (except from MTF) in media where drugs are highly ionized, the higher % of drug ionized resulted in increased reference drug solubilities in compendial (0.1 N HCl pH 1, phosphate buffer pH 6.8) compared to biorelevant media (FaSSGF pH 1.6, FaSSIF-V2 pH 6.5) [48].

Table 4.5: Reference solubility values (μg/mL) of the studied drugs at 24 hours in compendial and biorelevant media. (Mean ± SD)

	Compendial Media		**Biorelevant Media**	
Drug	**0.1 N HCl pH 1**	**Phosphate buffer pH 6.8**	**FaSSGF**	**FaSSIF-V2**
MTF	3.1×10^5 ($\pm0.3\times10^5$)	3.1×10^5 ($\pm0.2\times10^5$)	3.4×10^5 ($\pm0.8\times10^5$)	4.3×10^5 ($\pm0.4\times10^5$)
PRC	1.6×10^4 ($\pm 0.1\times10^4$)	1.5×10^4 ($\pm 0.1\times10^4$)	1.7×10^4 ($\pm 0.2\times10^4$)	1.7×10^4 ($\pm 0.1\times10^4$)
SMX	1.6×10^3 ($\pm 0.1\times10^3$)	3.7×10^3 ($\pm 0.1\times10^3$)	862 (±21)	1.3×10^3 ($\pm 0.1\times10^3$)
FRS	14 (±2)	3.4×10^3 ($\pm1.4\times10^2$)	15 (±1)	1.6×10^3 ($\pm3.0\times10^2$)
CBZ	265 (±6)	227 (±9)	368 (±1)	280 (±7)
DPL	1.3×10^4 ($\pm9.1\ 10^2$)	5 (±1)	8.6×10^3 ($\pm2.0\times10^2$)	13 (±1)
IBU	43 (±3)	5.5×10^3 ($\pm\ 6.7\times10^2$)	44 (± 5)	1.5×10^3 (± 5.8)
ITZ	11 (±1)	-*	1.2 (± 0.2)	0.05 (± 0.01)

*below limit of detection of the analytical method

SSG: The effects of the studied SSG brands on drug solubility at 24 hours in compendial and biorelevant media are presented in **Figures 4.2** and **4.3**, respectively. For MTF, in presence of 5% of Glycolys the solubility experiments resulted in the creation of a paste due to the high viscosity of the polymer in all media tested, therefore only results with the low Glycolys level are presented.

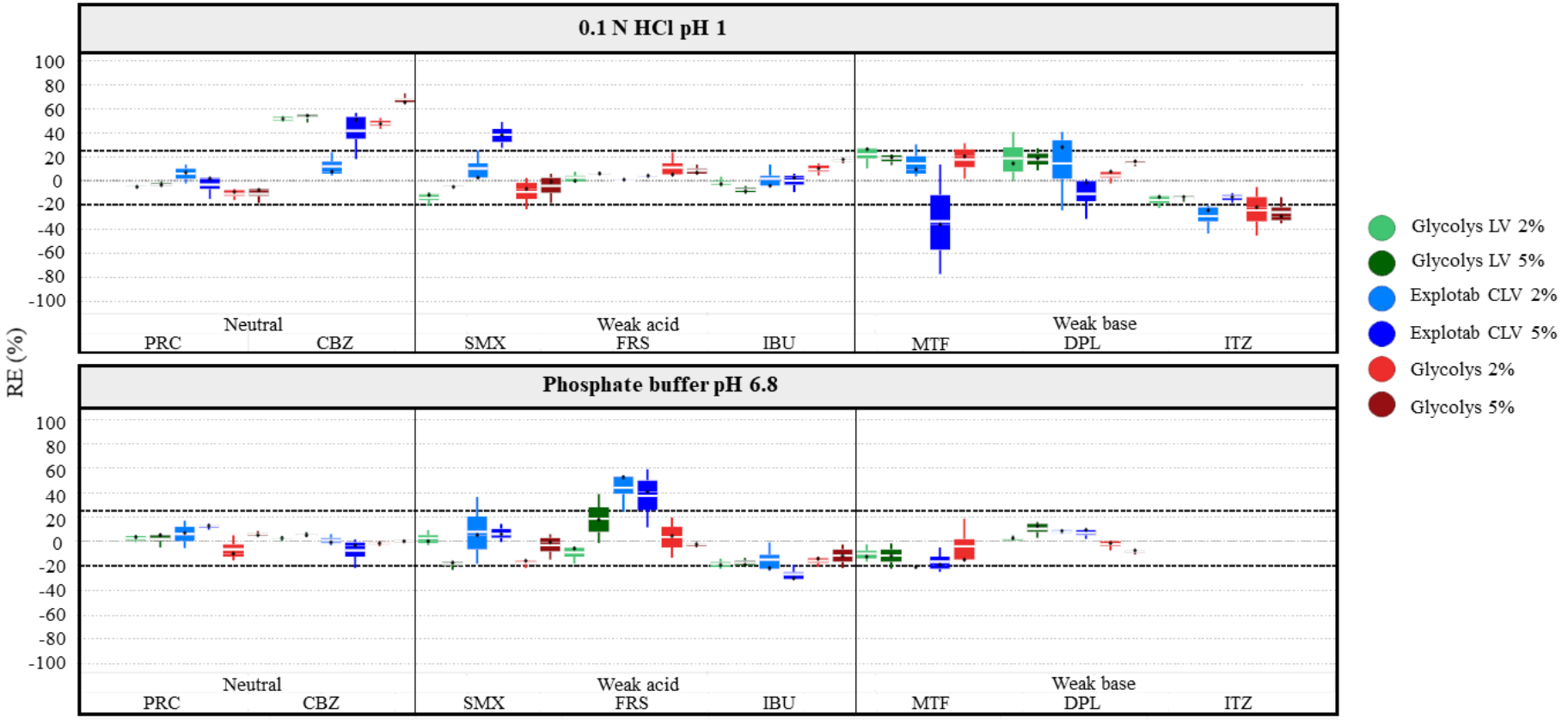


Figure 4.2: Box plots of the relative effects (%) of the studied SSG brands on drug solubility at 24 hours in compendial media. The excipient brands are shown as: i. Glycolys LV (green colour), ii. Explotab CLV (blue colour) and iii. Glycolys (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

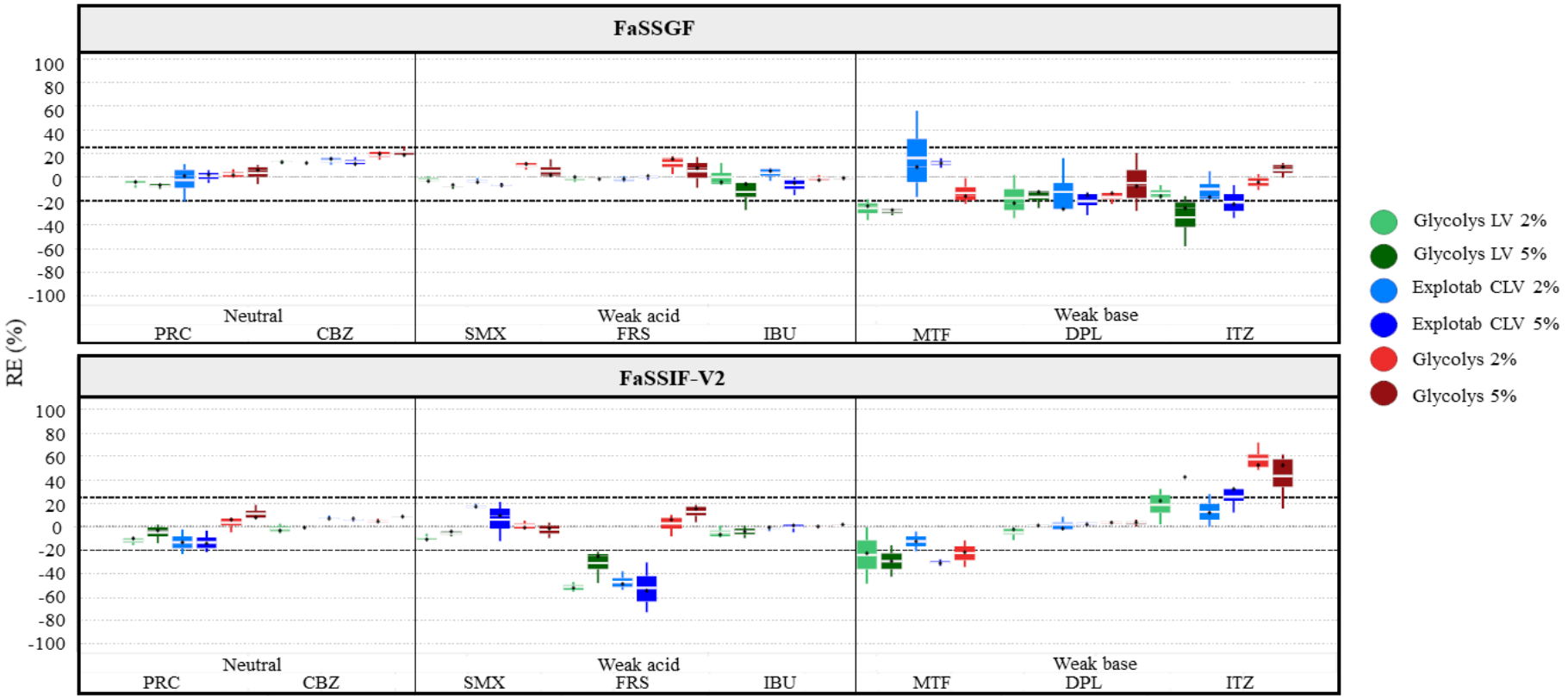


Figure 4.3: Box plots of the relative effects (%) of the studied SSG brands on drug solubility at 24 hours in biorelevant media. The excipient brands are shown as: i. Glycolys LV (green colour), ii. Explotab CLV (blue colour) and iii. Glycolys (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

Significant reduction in drug solubility at 24 hours by the low viscosity SSG brands (Glycolys LV, Explotab CLV) was observed for weak acids in FaSSIF-V2 and weak bases in media where drugs are highly ionized (-50% < REs < -20%). The high viscosity Glycolys significantly decreased the MTF solubility in FaSSIF-V2 (RE = -22%, low excipient level) and ITZ solubility in 0.1 N HCl pH 1 (REs of -23% and -25% for the low and high excipient level, respectively) at 24 hours. Reduction in the pH of basic media for weak acids (0.2 – 0.7 pH units) was observed (attributed to the drug ionization) in the cases where SSG significantly decreased drug apparent solubility. Changes in the pH of the media cannot justify the differences in drug solubility at 24 hours for weak acids in excipient presence as experimental drug solubility values do not correspond to the theoretical equilibrium solubility values (expected by the change in the pH of the medium and the design of the pH-solubility profiles) (**Figure 4.4**). Increase in the pH of acidic media for weak bases (0.2 – 4 pH units) was observed in the cases where SSG presence significantly decreased drug solubility (attributed to drug ionization) however the impact of pH on the weak basic compound solubility at 24 hours cannot be assessed due to *in situ* salt formation between the API and counterions of the medium [49]. Presence of insoluble excipients may delay drug dissolution and/or drug solubilization as their insolubility or variable "wetting" characteristics result in reduced drug-medium contact [50]. Therefore, the observed reduction in drug apparent solubility by SSG could relate to a shielding excipient effect on powder surface which further limits drug dissolution and/or drug solubilization. Cases of decreased drug solubility at 24 hours were mostly observed in presence of low viscosity SSG brands (Glycolys LV, Explotab CLV) compared to the high viscosity Glycolys and could be explained by the extensive swelling of low viscosity brands [9] which creates a barrier for drug dissolution from the powder surface. For neutral drugs, significant increase in drug apparent solubility was observed for CBZ in 0.1 N HCl pH 1 (42% < REs < 67%) in presence of all the studied brands. Changes in the pH of the media were not observed in the case of CBZ in excipient presence or absence. Solubility data of CBZ at 0.5, 4 and 24 hours in absence and presence of the studied SSG brands in compendial and biorelevant media are presented in **Figure 4.5a**. The solubility of pure CBZ decreased through time in compendial media (350 μg/mL and 250 μg/mL at 0.5 hours and 24 hours, respectively), potentially due to drug aggregation [51] or due to the conversion of CBZ

anhydrate to CBZ dihydrate in solution (solution mediated phase transformation) [52, 53]. This reduction in CBZ apparent solubility is not observed in presence of SSG, as potentially dissolved polymer particles may enhance drug solubilization and delay drug aggregation [54]. Inhibition of the solution mediated phase transformation of CBZ in excipient presence due to the interaction of the amine group of CBZ with the carboxylic group of SSG (**Figure 4.1**), could also explain the fact that CBZ solubility was not reduced in excipient presence [52, 53] and justify the less pronounced impact of SSG in phosphate buffer pH 6.8 compared to 0.1 N HCl pH 1 (as the increased excipient hydrophilicity (due to excipient ionization [8]) would decrease the likelihood of drug-excipient interaction [55]). For weak acids, significant increase in drug solubility at 24 hours was observed in presence of Explotab CLV for SMX in 0.1 N HCl pH 1 (high excipient level: RE = 38%) and FRS in phosphate buffer pH 6.8 (REs of 44% and 37% for the low and high level, respectively). In both cases, the reduction in the pH of the medium was higher in presence (SMX: 0.2 pH units, FRS: 0.3 pH units) compared to excipient absence (SMX: 0.06 pH units, FRS: 0.2 pH units). Evaluation of the theoretical pH-solubility profiles (**Figure 4.4**) revealed that in SSG presence, the experimental drug solubility corresponds to the theoretical equilibrium solubility (expected by the change in the pH of the medium), therefore the aforementioned cases of increased solubility are attributed to the shift in the pH of the medium (further investigations on the impact of dissolved drugs or excipients on the pH of the medium are needed to explain the nature of this change, as reduction in the pH of the medium by SSG is not expected). For weak bases, significant increase in drug apparent solubility was observed for ITZ in FaSSIF-V2 in presence of the high excipient level of low viscosity brands (REs of 42% and 25% for Glycolys LV and Explotab CLV, respectively) and both levels of the high viscosity Glycolys (REs of approximately 50% for both excipient levels). Changes in the pH of the medium in presence of SSG were not observed in this case, despite the ionization pattern of the excipient potentially due to the buffer capacity of the medium (10 mM/dpH) [47]. ITZ forms a supersaturated solution in FaSSIF-V2 due to the micellar solubilization effect of bile salts and slowly precipitates with time [56]. The increase in ITZ solubility at 24 hours in SSG presence in FaSSIF-V2 can be attributed to the inhibition of drug precipitation by the polymeric chains of SSG. The increase in ITZ solubility was more pronounced in presence of the high compared to the low viscosity brands, as

potentially high viscosity excipients have a better ability in delaying particle agglomeration and improve drug solubilization [57].

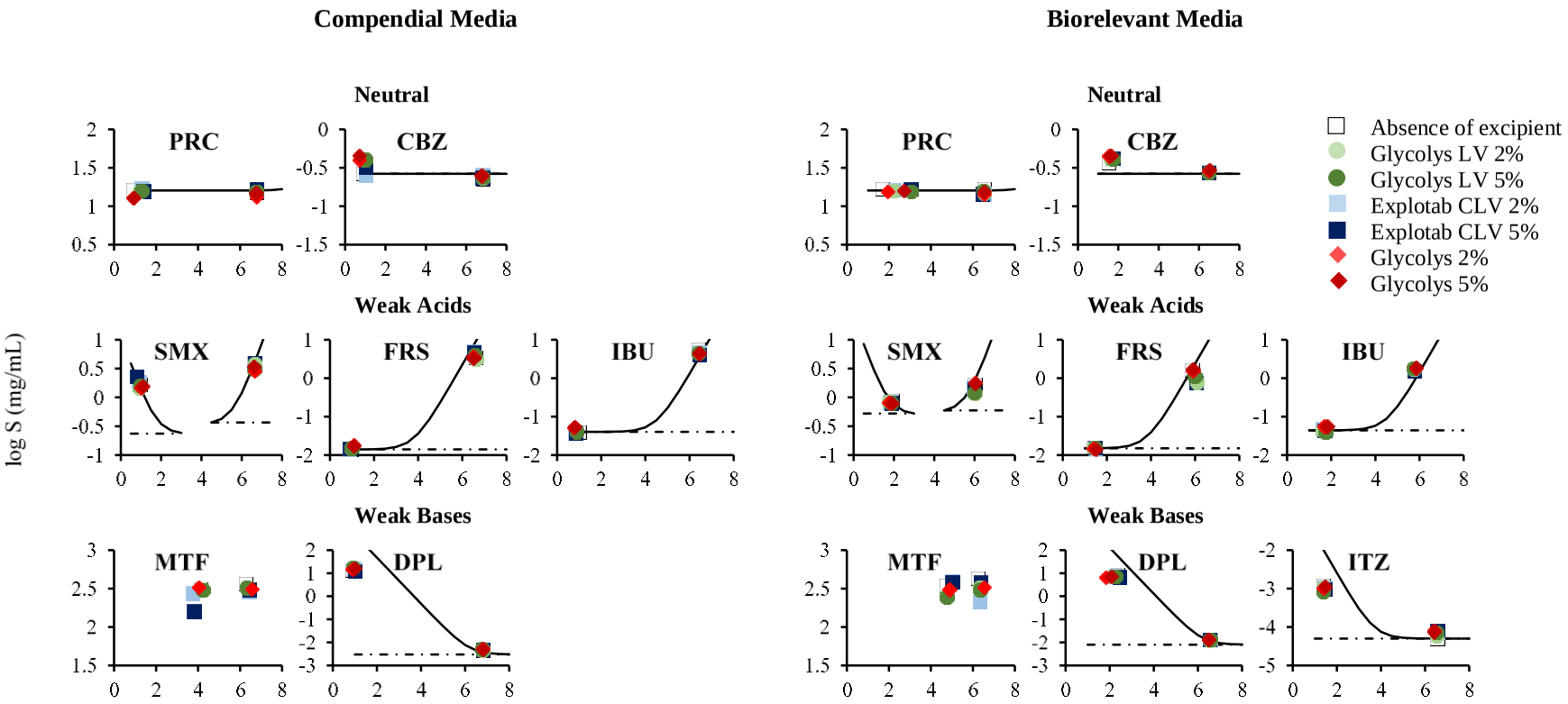


Figure 4.4: Theoretical pH-solubility profiles of the studied drugs in compendial and biorelevant media and experimental drug solubility values in absence (squares) and presence of excipients (i. Glycolys LV (green colour), ii. Explotab CLV (blue colour), iii. Glycolys (red colour)). Dashed lines indicate drug intrinsic solubility.

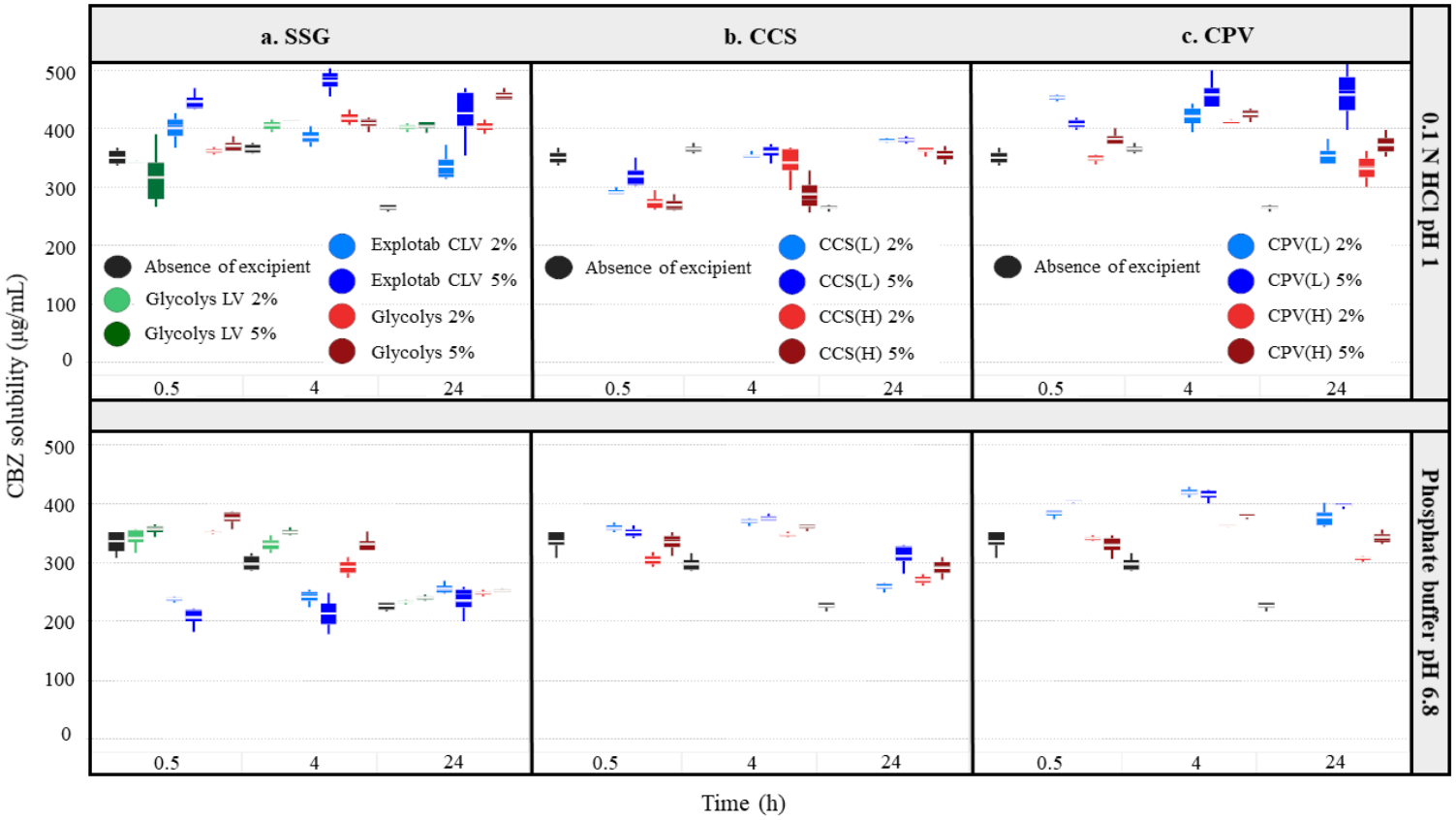


Figure 4.5: Box plots of CBZ solubility (µg/mL) in absence (black colour) and presence of the studied a. SSG (i. Glycolys LV (green colour), ii. Explotab CLV (blue colour), iii. Glycolys (red colour)), b CCS (i. CCS(L) (blue colour), ii. CCS(H) (red colour) and iii. CPV (CPV(L) (blue colour), ii. CPV(H) (red colour)) brands in 0.1 N HCl pH 1 and phosphate buffer pH 6.8. Light and dark colours correspond to low and high excipient level, respectively. (Mean, n = 3)

CCS: Cases of significant decrease in the solubility of weak acids and weak bases at 24 hours were mostly observed in media where drugs are highly ionized (CCS(L): -50% < REs < -20%, CCS(H): -62% < REs < -20%) (**Figures 4.6 and 4.7**). Reduction in drug apparent solubility was also observed for ITZ in FaSSIF-V2 by the low level of CCS(H) (RE = -40%) (**Figure 4.7**). In the cases of significant decrease in drug solubility by CCS at 24 hours, changes in the pH of the media (0.2 – 0.7 pH units reduction in basic media for weak acids, 0.2 – 4 pH units increase in acidic media for weak bases) are attributed to drug ionization and cannot explain the differences in drug solubility in presence of CCS (for weak acids) or be evaluated (for weak bases), as explained previously in the case of SSG (**Figure 4.8**). The slow drug dissolution and/or drug solubilization by the presence of CCS particles on the surface of the powder could justify the pronounced decrease in drug apparent solubility by CCS [50]. Significant increase in drug solubility at 24 hours for neutral drugs was observed in the case of CBZ in 0.1 N HCl pH 1 (32% < REs < 43% for both levels of CCS(L) and CCS(H)) and in phosphate buffer pH 6.8 (RE = 37% for the high level of CCS(L)). As changes in the pH of the media in excipient presence were not observed for CBZ, the differences in CBZ solubility in presence and absence of CCS are attributed to the enhanced drug solubilization or inhibition of drug solution-mediated phase transformation by the excipient [55] (**Figure 4.5b**). For weak acids, significant increase in SMX solubility at 24 hours was observed in 0.1 N HCl pH 1 in presence of 5% CCS(H) (RE = 45%) and is attributed to the change in the pH of the medium, as the reduction in the pH of the medium was higher in presence (0.3 pH units) compared to absence of 5% CCS(H) (0.06 pH units) and the experimental and theoretical drug solubility in excipient presence are similar (**Figure 4.8**) (further investigations on the impact of dissolved drug or excipient on the pH of the medium are needed to explain the nature of this change, as reduction in the pH of the medium by CCS is not expected). For weak bases, significant increase in drug apparent solubility was observed for ITZ in FaSSIF-V2 in presence of 5% CCS(H) (RE = 31%) which could be justified by the enhanced drug solubilization by the excipient.

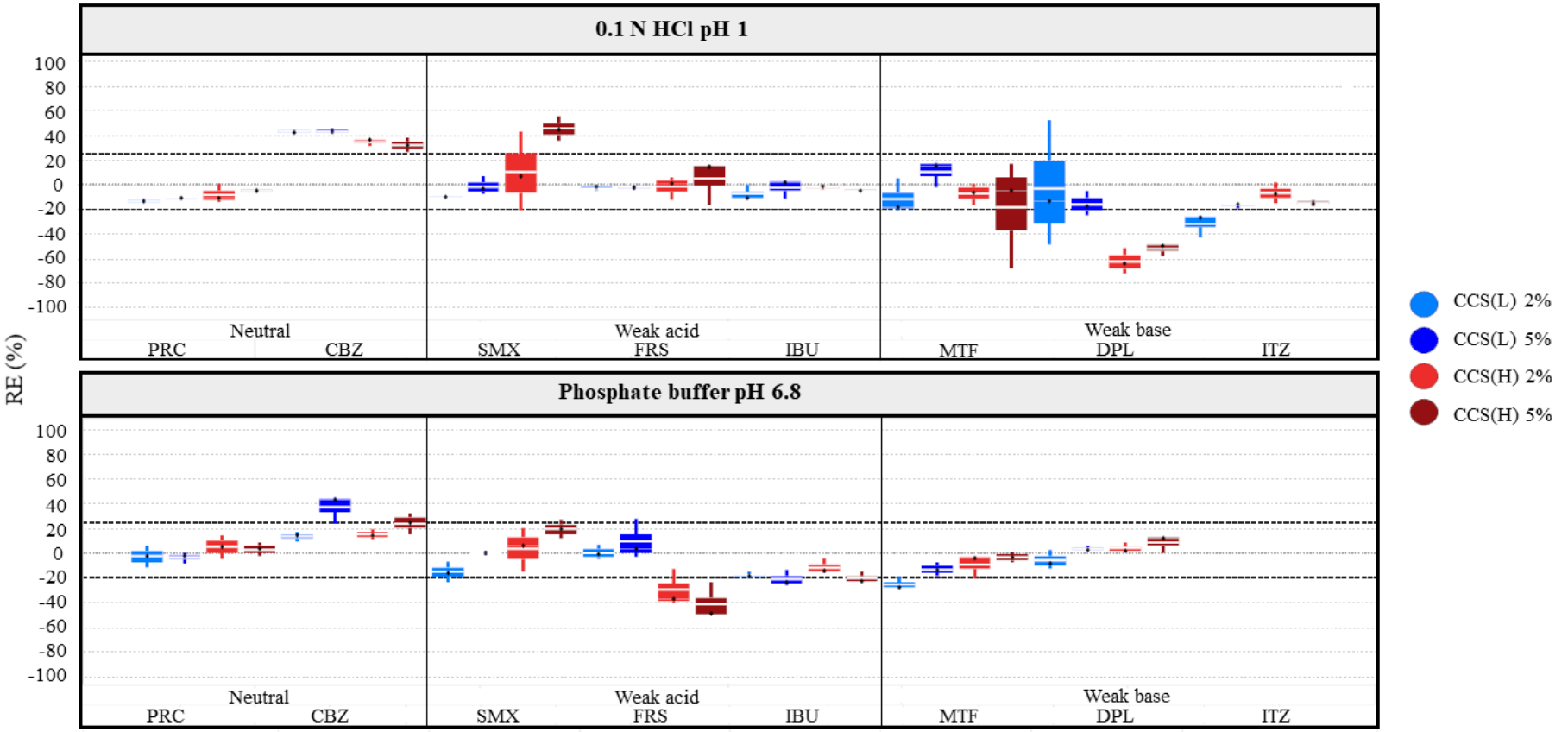


Figure 4.6: Box plots of the relative effects (%) of the studied CCS brands on drug solubility at 24 hours in compendial media. The excipient brands are shown as: i. CCS(L) (blue colour) and ii. CCS(H) (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

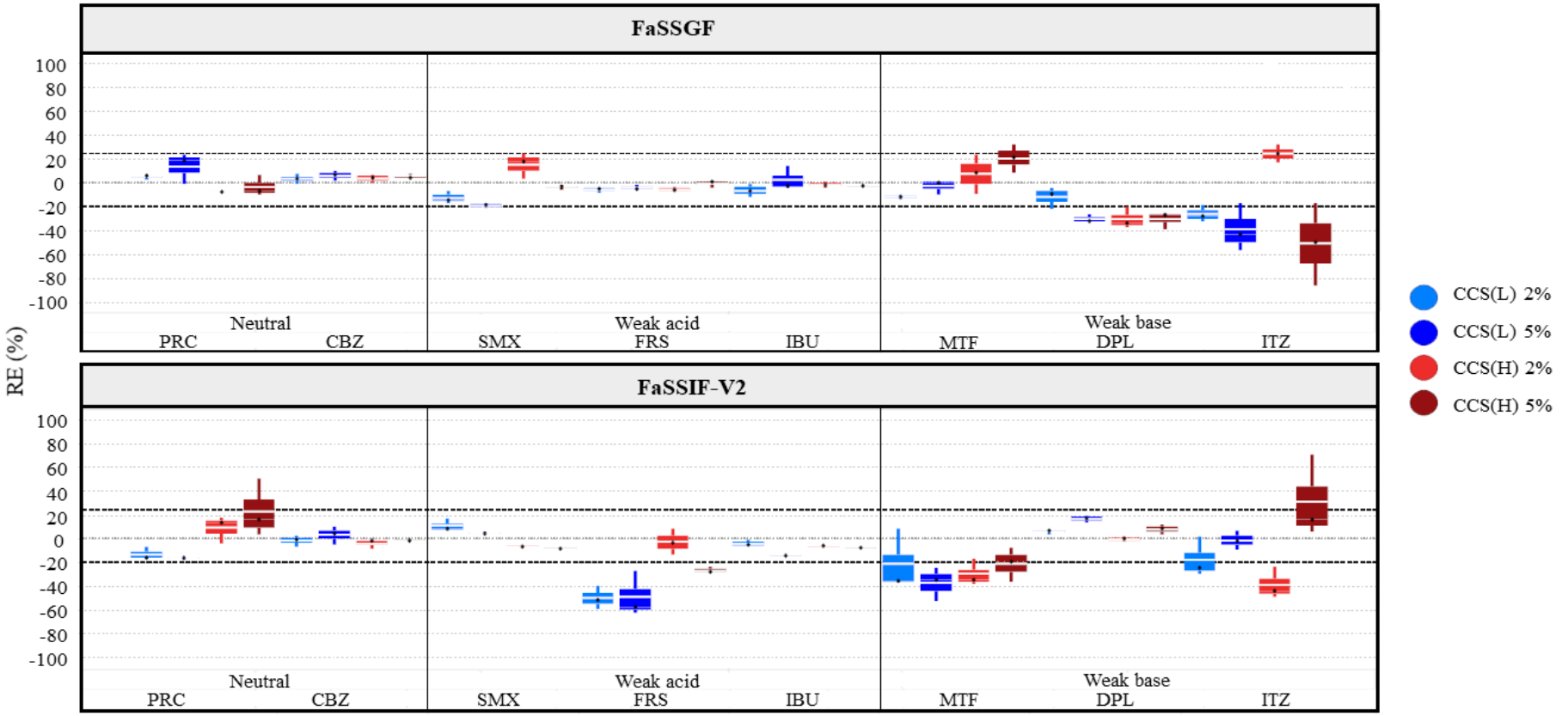


Figure 4.7: Box plots of the relative effects (%) of the studied CCS brands on drug solubility at 24 hours in biorelevant media. The excipient brands are shown as: i. CCS(L) (blue colour) and ii. CCS(H) (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

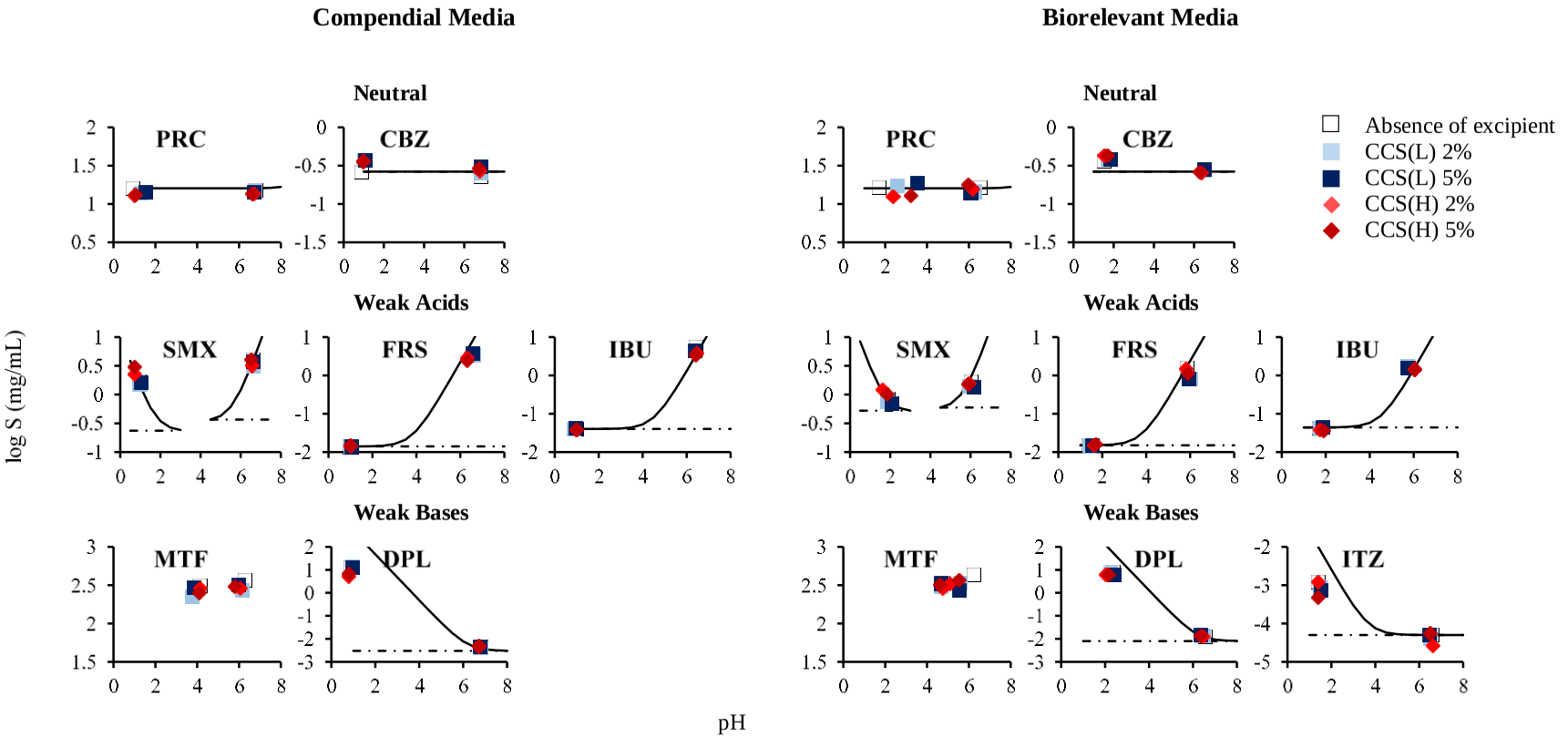


Figure 4.8: Theoretical pH-solubility profiles of the studied drugs in compendial and biorelevant media and experimental drug solubility values in absence (squares) and presence of excipients (i. CCS(L) (blue colour), ii. CCS(H) (red colour)). Dashed lines indicate drug intrinsic solubility.

CPV: Cases of significant reduction in drug solubility at 24 hours by CPV presence was observed for weak acids and weak bases in media where drugs are highly ionized (CPV(L): -50% < REs < -20%, CPV(H): -40% < REs < -21%) (**Figures 4.9 and 4.10**). Reduction in drug apparent solubility was also observed in the case of ITZ in FaSSIF-V2 in presence of both CPV brands (-30% < REs < -20%) (**Figure 4.10**). In the case of significant reduction in drug solubility by CPV, the ionization of drugs resulted in reduction in the pH of the basic media for weak acids (0.2 – 0.7 pH units) or increase in the pH of acidic media for weak bases (0.2 – 4 pH units). The observed changes in the pH of the media cannot explain the differences in drug solubility at 24 hours in CPV presence (**Figure 4.11**), as explained previously for SSG and CCS. Therefore, the pronounced reduction in drug apparent solubility by CPV is justified by the presence of the insoluble excipient on the powder surface [50]. For neutral drugs, significant increase in drug solubility at 24 hours was observed in the case of CBZ in compendial media (25% < REs < 56%) and is attributed to the enhanced drug solubilization or inhibition of drug solution mediated phase transformation by the excipient (**Figure 4.5c**) [55]. For weak acids, significant increase in drug solubility at 24 hours was observed for FRS in phosphate buffer pH 6.8 in presence of both levels of CPV(L) (REs ≈ 70%). This pronounced increase in FRS solubility is justified by the change in the pH of the medium, as the reduction in the pH of the medium was higher in excipient presence (0.4 pH units) compared to excipient absence (0.2 pH units) (**Figure 4.11**) (further investigations are needed to explain the nature of this change, as changes in the pH of the medium by the non-ionic CPV are not expected). For weak bases, significant increase in the apparent solubility of MTF was observed in 0.1 N HCl pH 1 in presence of the high level of CPV(H) (RE = 63%). The increase in the pH of the medium in absence and presence of excipient was similar (3 pH units) and is attributed to the protonation of MTF. As changes in the pH of the media for weak bases cannot be evaluated, further investigations are needed to explain the pronounced increase in MTF solubility.

The solubility data showed increased variability in the cases where superdisintegrant presence significantly affected drug solubility (MTF: CV% > 30%, PRC or highly ionized poorly soluble drugs: 20% < CV% < 40%). As working with physical mixtures may yield high standard deviations due to the heterogeneous

dispersion of the constituents [58, 59], the increased variability can be attributed to the heterogeneous saturation of powder surface with excipient particles.

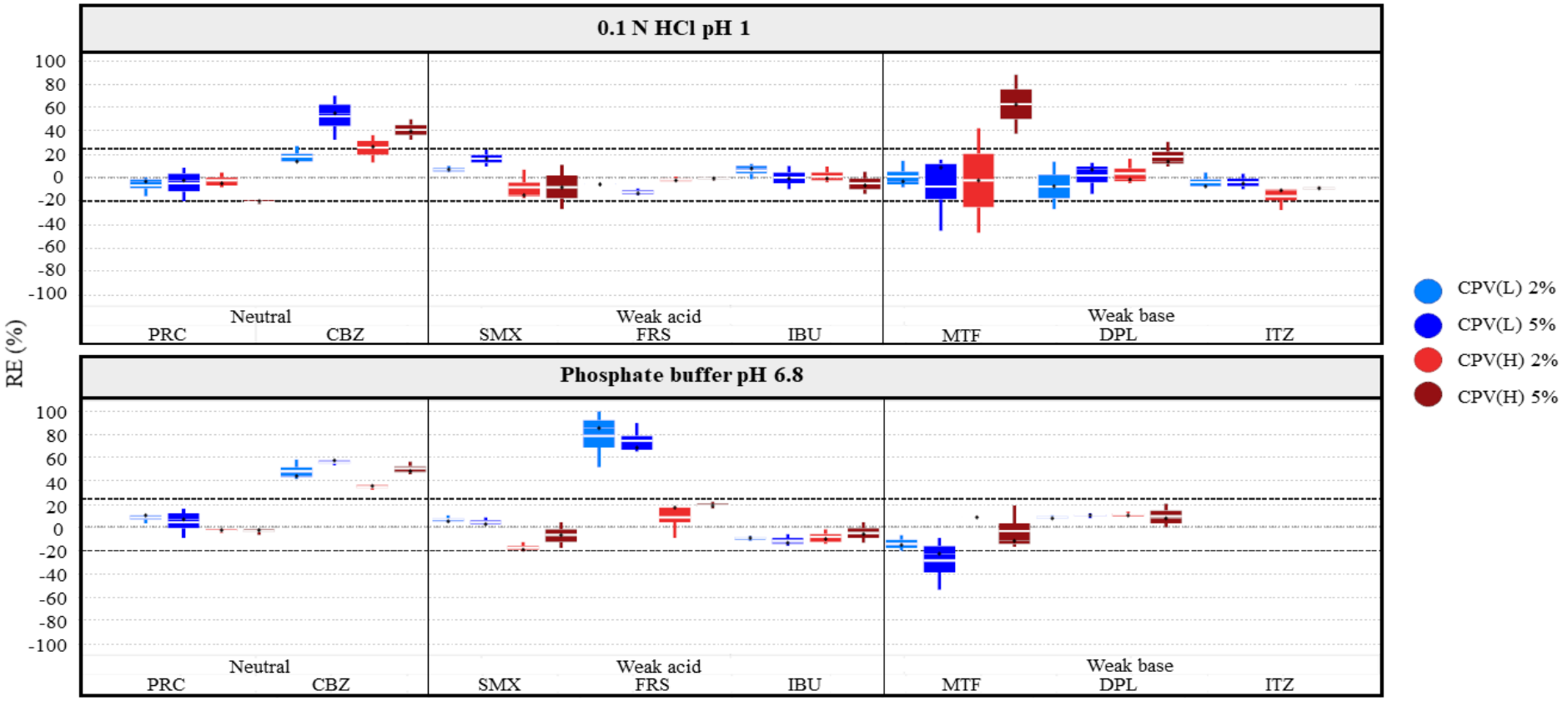


Figure 4.9: Box plots of the relative effects (%) of the studied CPV brands on drug solubility at 24 hours in compendial media. The excipient brands are shown as: i. CPV(L) (blue colour) and ii. CPV(H) (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

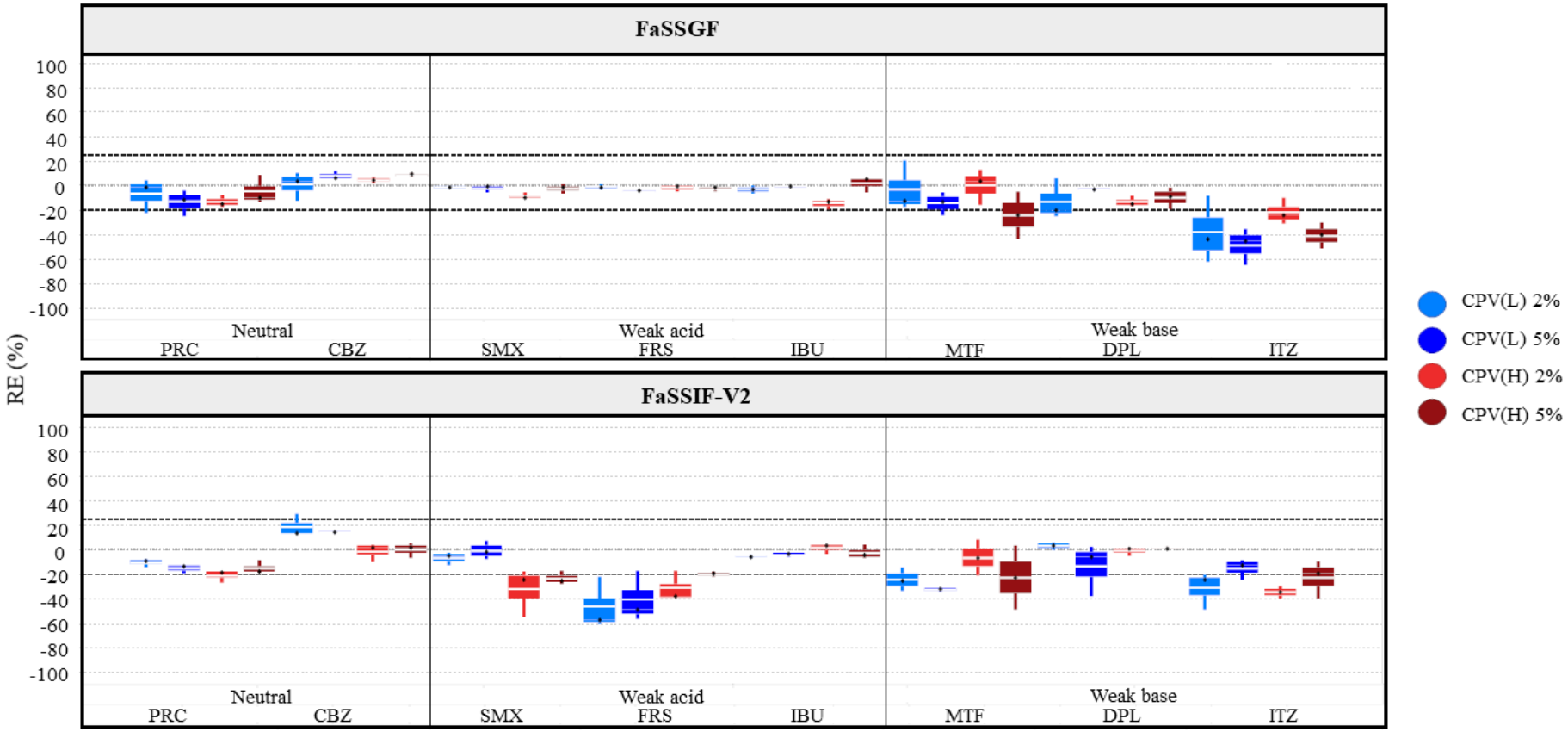


Figure 4.10: Box plots of the relative effects (%) of the studied CPV brands on drug solubility at 24 hours in biorelevant media. The excipient brands are shown as: i. CPV(L) (blue colour) and ii. CPV(H) (red colour). Light and dark colours correspond to low and high excipient level, respectively. (Mean (white line), Median (black diamond), n = 3)

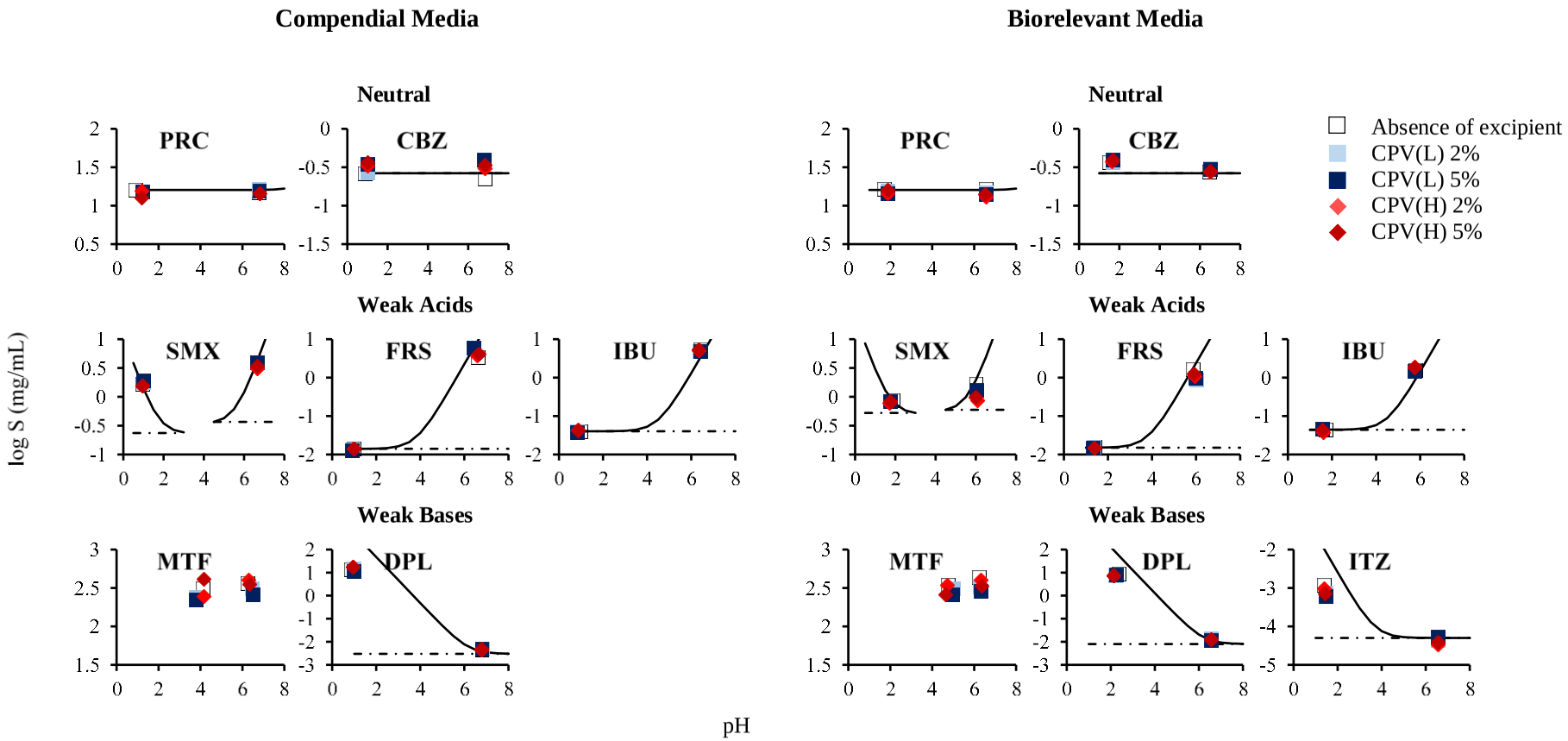


Figure 4.11: Theoretical pH-solubility profiles of the studied drugs in compendial and biorelevant media and experimental drug solubility values in absence (squares) and presence of excipients (i. CPV(L) (blue colour), ii. CPV(H) (red colour)). Dashed lines indicate drug intrinsic solubility.

4.3.2.2. Impact of excipients on drug apparent solubility based on drug physicochemical properties

The effects of the studied superdisintegrants on drug solubility at 24 hours as a function of drug ionization and drug lipophilicity in compendial and biorelevant media are presented in **Figure 4.12**.

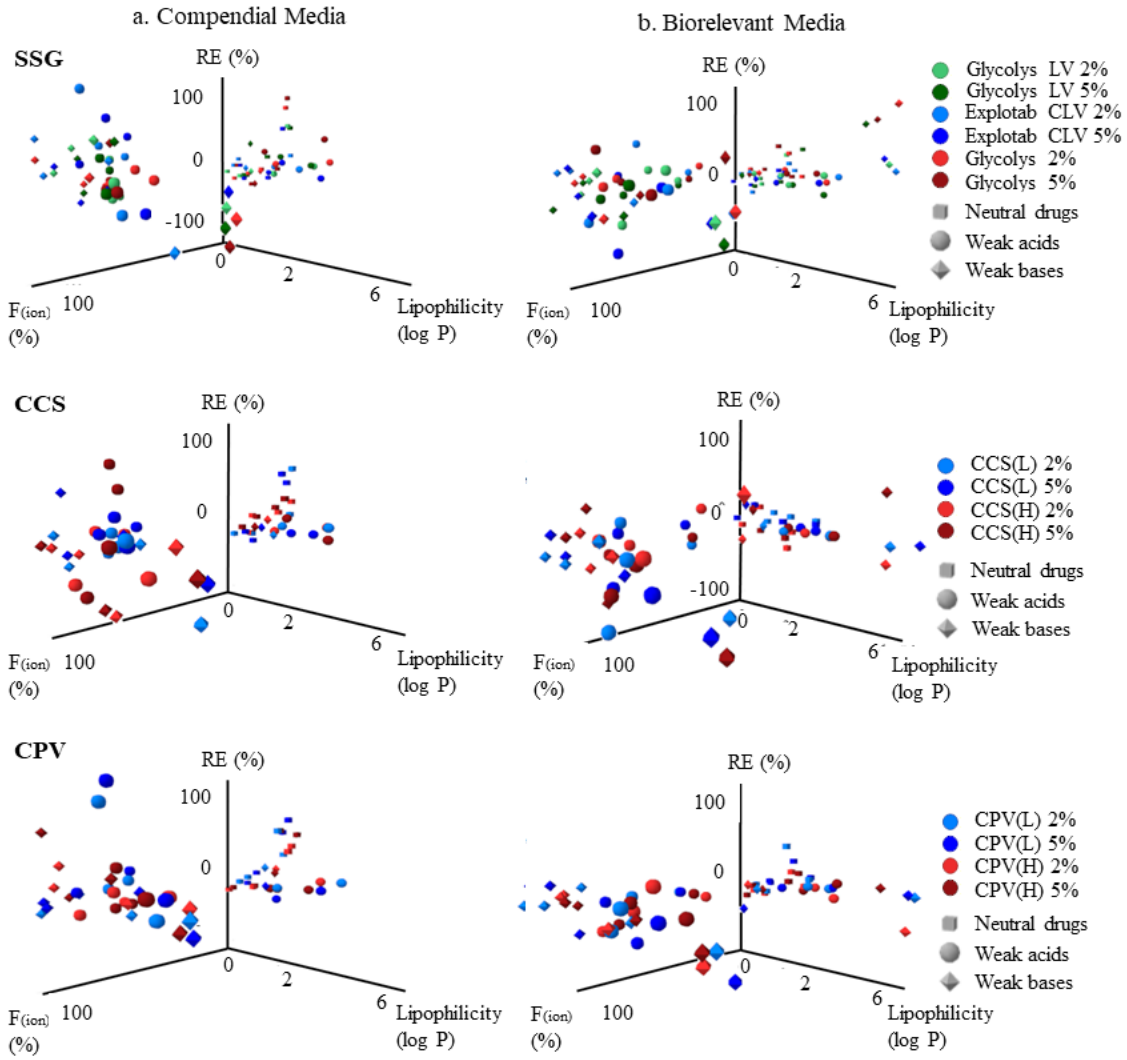
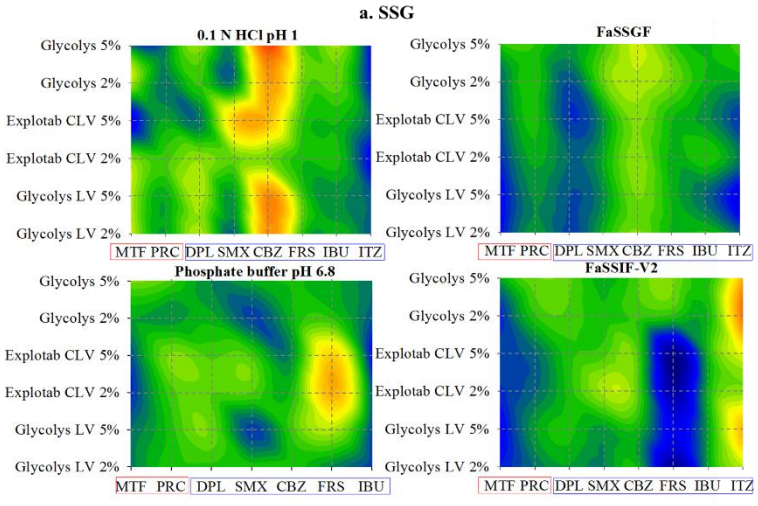


Figure 4.12: Relative effects (%) of the studied SSG (i. Glycolys LV (green colour), ii. Explotab CLV (blue colour), iii. Glycolys (red colour)), CCS (i. CCS(L) (blue colour), ii. CCS(H) (red colour)) and CPV (i. CPV(L) (blue colour), ii. CPV(H) (red colour)) brands on drug solubility at 24 hours as a function of drug ionization (%) and drug lipophilicity (log P) in a. compendial and b. biorelevant media. Light and dark colours correspond to low and high excipient level, respectively.

The reduction in drug apparent solubility by superdisintegrant presence is more pronounced in media (compendial or biorelevant) where drugs are highly ionized (excluding the cases of increased drug solubility attributed to the change in the pH of the medium), potentially due to the presence of a high number of excipient particles on the powder surface which limits drug dissolution and/or drug solubilization [50] (as explained previously in Chapters 2 and 3). For the ionic superdisintegrants (SSG, CCS), interactions between ionized drugs and the excipient polymeric chains [17, 60] may also have contributed to the observed reduction in drug solubility at 24 hours. A trend between the impact of superdisintegrants on drug solubility and drug lipophilicity was not observed, apart from the case of SSG in biorelevant media, where increase in drug solubility was observed with increasing drug lipophilicity (when drugs are in the low ionization state). The classification gradient maps depicting the effects of the studied superdisintegrants on drug solubility at 24 hours as a function of drug aqueous solubility in compendial and biorelevant media is presented in **Figure 4.13**. A clear trend between the reduction in drug apparent solubility by excipient presence and drug aqueous solubility cannot be observed.



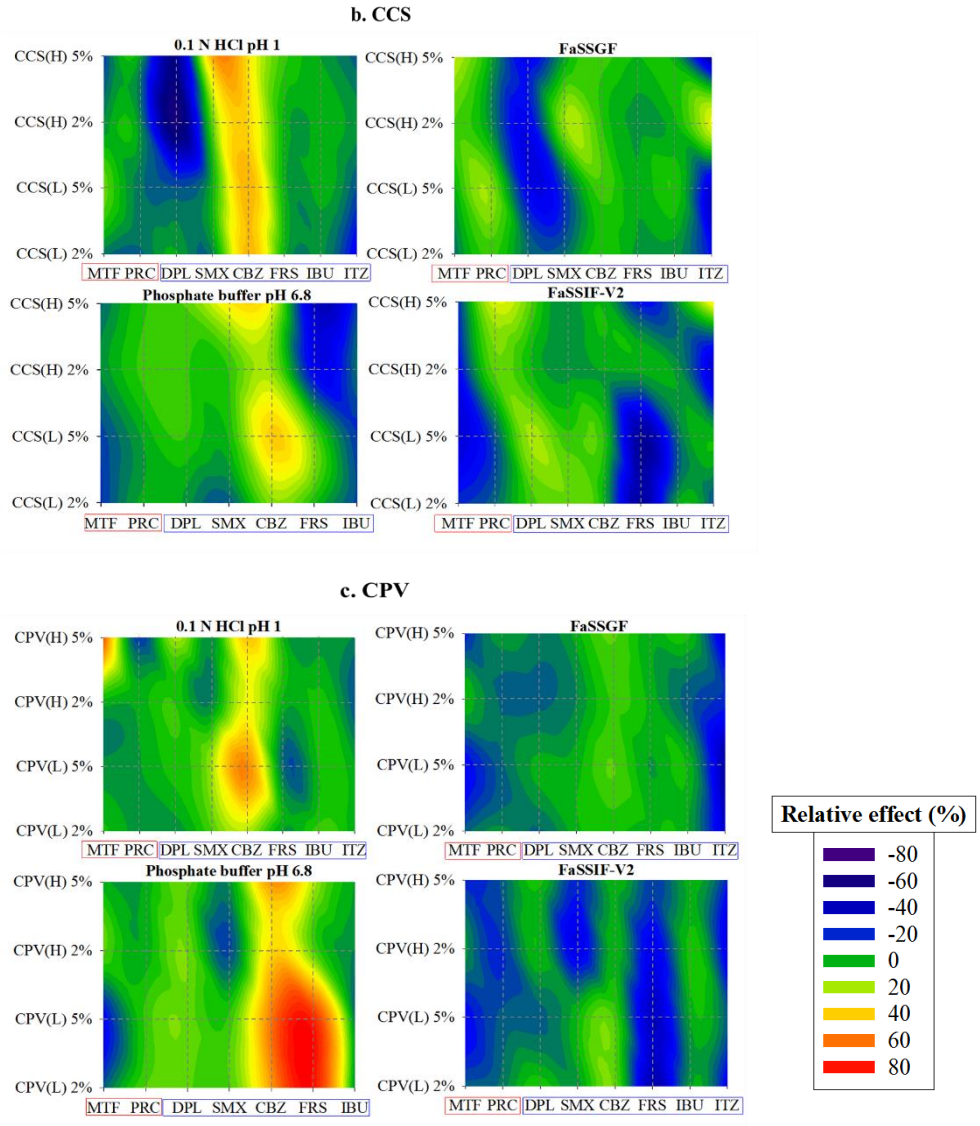


Figure 4.13: Classification gradient maps of the relative excipient effects of the a. SSG, b. CCS and c. CPV brands on the solubility of highly and poorly soluble compounds at 24 hours. Y-axes are set in an increasing viscosity and level order for SSG and increasing particle size and level order for CCS and CPV. The x-axes are set in a decreasing drug aqueous solubility order (red colours for highly soluble and blue colours for poorly soluble drugs).

4.3.3. Multivariate Data Analysis

For SSG, the two models showed an average fit (compendial media: $Q^2 = 0.3$, $R^2 = 0.4$ and biorelevant media: $Q^2 = 0.5$, $R^2 = 0.6$) (**Figure 4.14**). The statistical model reveals that the impact of SSG on drug apparent solubility depends on drug

physicochemical properties. Amine group (compendial media: positive effect, VIP = 2.6, biorelevant media: positive effect, VIP = 2.2) was a significant variable in both sets of media indicating that significant increase in drug solubility at 24 hours is anticipated in SSG presence for drugs containing a neutral amine due to potential drug-SSG interaction which improves drug solubilization [55]. Drug ionization (compendial media: negative effect, VIP = 2.3, biorelevant media: negative effect, VIP = 2.5) was an influential variable in both models indicating that significant reduction in drug apparent solubility in SSG presence is expected for highly ionized drugs due to the saturation of powder surface with excipient particles [50] or drug-SSG interactions [17] which delay drug dissolution and/or drug solubilization. In biorelevant media, drug lipophilicity (positive effect, VIP = 1.4) and drug solubility (negative effect, VIP = 1.1) were significant variables in the model. These variables indicate that pronounced increase in the apparent solubility of poorly soluble/lipophilic drugs can be observed in presence of SSG as a result of enhanced drug solubilization. The negative effect of drug solubility can also indicate a reduction in drug solubility at 24 hours for highly soluble drugs due to the saturation of powder surface with excipient particles [50] (as for highly soluble drugs, drug molecules can dissolve faster in the medium especially in the presence of solubilizing components [47]). The impact of excipient properties on drug apparent solubility was found critical only in biorelevant media as demonstrated by the significance of the term exc. brand (positive effect, VIP = 1.4) in the model. This term reveals that the increase in drug solubility at 24 hours will be more pronounced in presence of high viscosity SSG brands as potentially high viscosity excipients have a better ability in delaying particle agglomeration and improve drug solubilization [57].

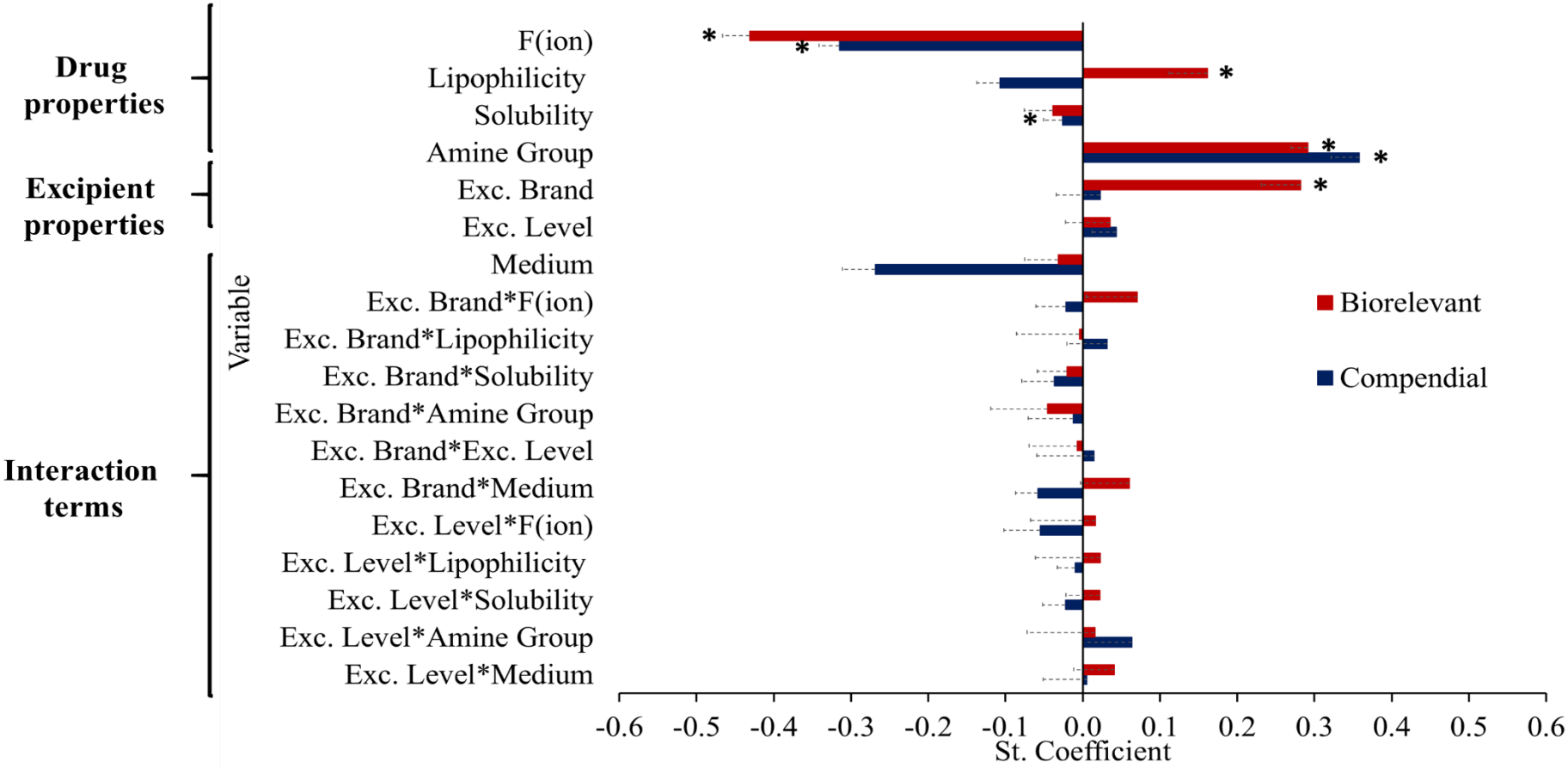


Figure 4.14: Standardized coefficients of the studied variables (and interaction terms) in compendial (blue colour) and biorelevant (red colour) media for SSG. * denotes coefficients of VIP > 1. * denotes coefficients of 0.8 < VIP < 1. (Mean, - SE)

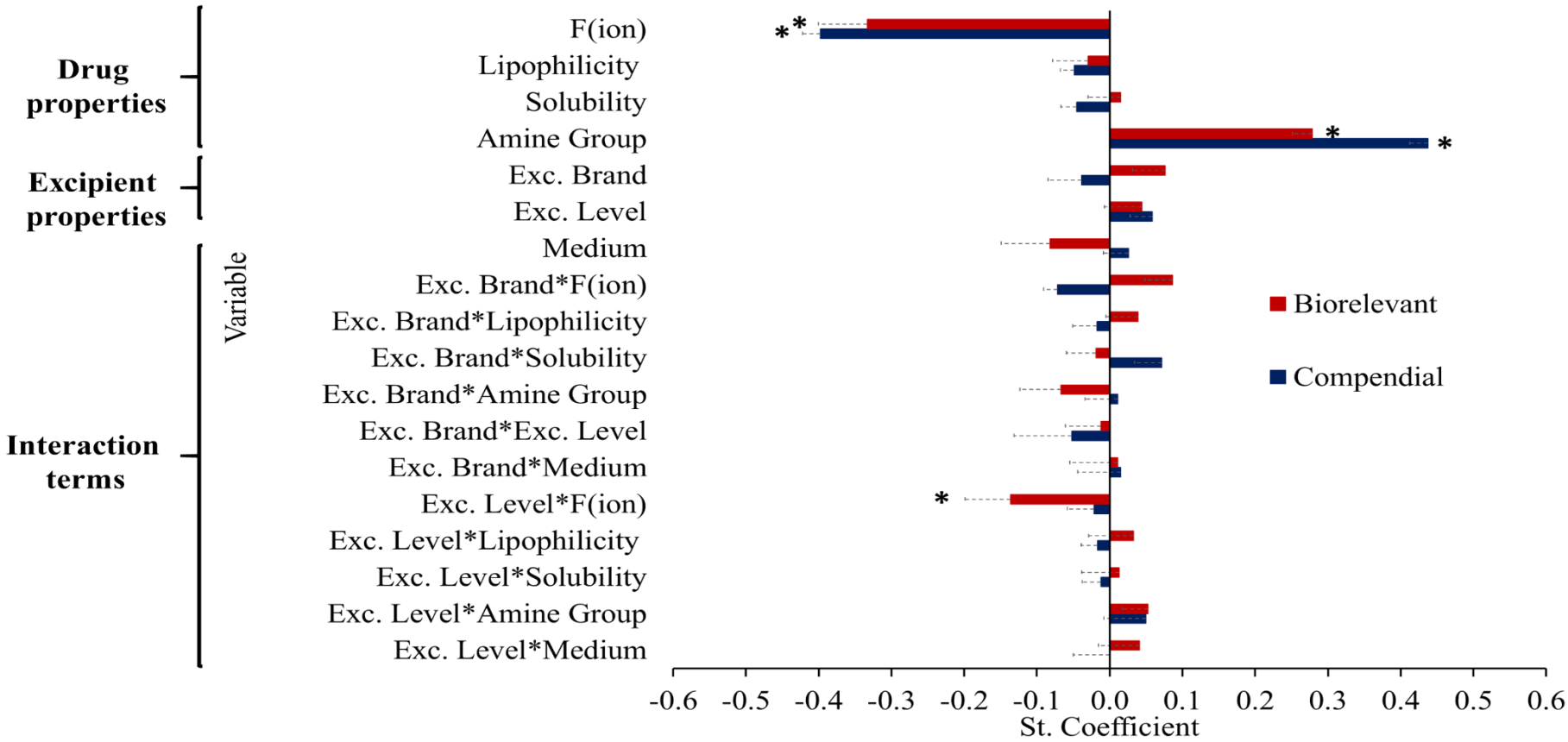


Figure 4.15: Standardized coefficients of the studied variables (and interaction terms) in compendial (blue colour) and biorelevant (red colour) media for CCS. * denotes coefficients of VIP > 1. * denotes coefficients of 0.8 < VIP < 1. (Mean, - SE)

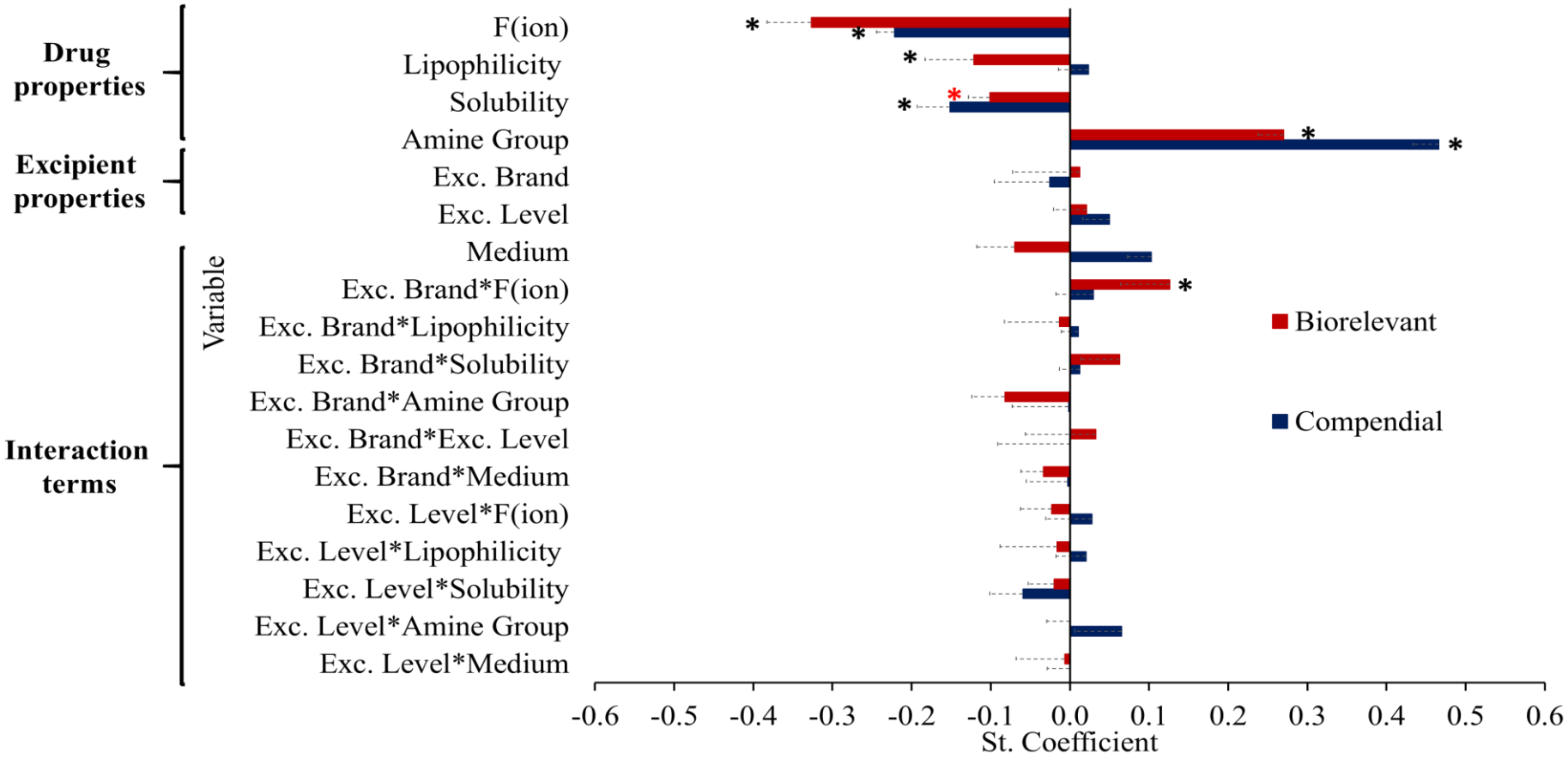


Figure 4.16: Standardized coefficients of the studied variables (and interaction terms) in compendial (blue colour) and biorelevant (red colour) media for CPV. * denotes coefficients of VIP > 1. * denotes coefficients of 0.8 < VIP < 1. (Mean, - SE)

For CCS, average fittings (compendial media: Q^2 = 0.5, R^2 = 0.6, biorelevant media: Q^2 = 0.2, R^2 = 0.3) were obtained (**Figure 4.15**). Amine group (compendial media: positive effect, VIP = 3.0, biorelevant media: positive effect, VIP = 2.4) and drug ionization (compendial media: negative effect, VIP = 2.7, biorelevant media: negative effect, VIP = 2.8) were significant factors in both sets of media. The variable amine group indicates that significant increase in the apparent solubility of drugs containing a neutral amine group is expected as a result of the enhanced drug solubilization by CCS presence due to a potential drug-CCS interaction which improves drug solubilization [55]. The negative effect of drug ionization reveals that pronounced reduction in the apparent solubility of highly ionized drugs will be anticipated in presence of CCS due to the saturation of the powder surface by excipient particles [50] or drug-CCS interactions [17] which limit drug dissolution and/or drug solubilization. Excipient properties can be critical factors for the impact of CCS on drug solubility in biorelevant media, as demonstrated by the significance of the variable excipient level*drug ionization (negative effect, VIP = 1.1) in the model. As the presence of solubilizing components improves powder wettability and drug solubilization [47], the high number of excipient particles on top of the powder surface or the extensive excipient swelling when increasing CCS level will result in higher reduction in the apparent solubility of highly ionized drugs.

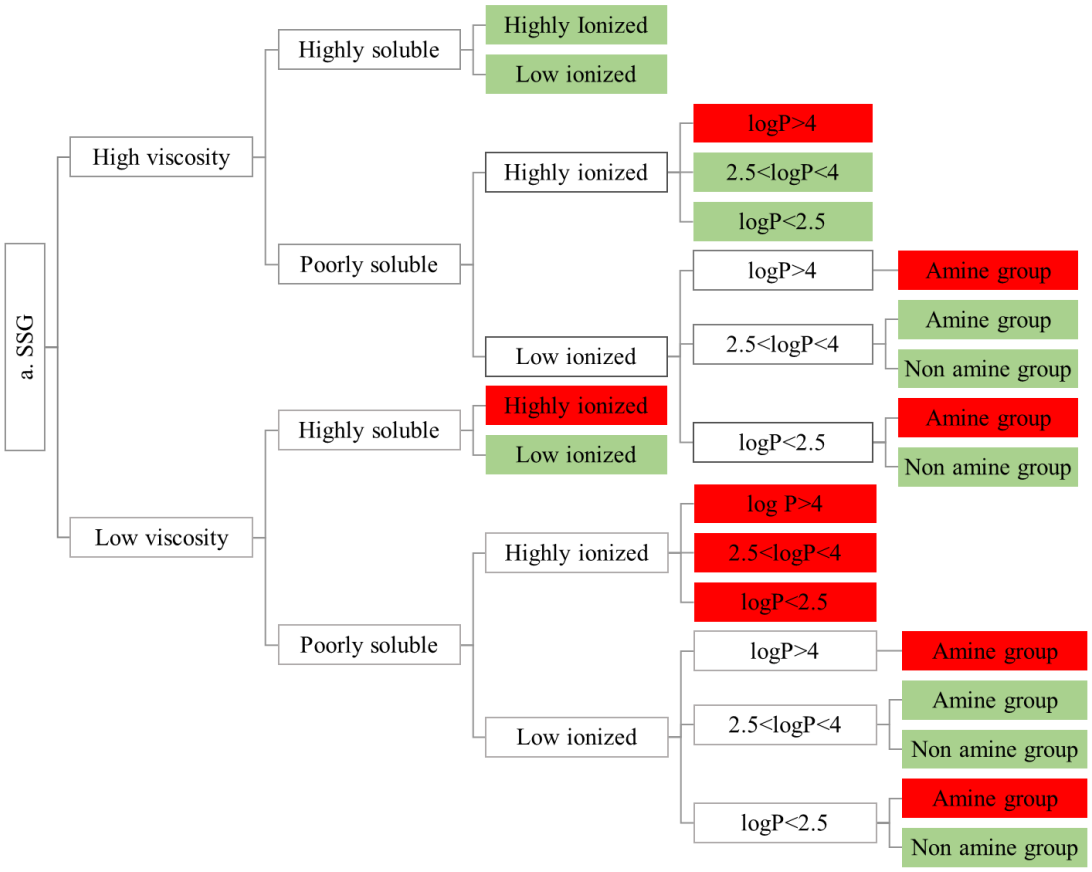
For CPV, average fits were observed (compendial media: Q^2 = 0.4, R^2 = 0.5 and biorelevant media: Q^2 = 0.2, R^2 = 0.3) (**Figure 4.16**). Drug physicochemical properties were critical parameters for the impact of CPV on drug apparent solubility. Amine group (compendial media: positive effect, VIP = 3.5, biorelevant media: positive effect, VIP = 2.3) was a significant variable in both models indicating that CPV is able in inhibiting drug agglomeration [55]. Drug ionization (compendial media: negative effect, VIP -1.6, biorelevant media: negative effect, VIP = 1.0) and drug solubility (compendial media: negative effect, VIP = 1.1, biorelevant media: negative effect, VIP = 0.8) were significant variables in both models. Both variables indicate that significant reduction in drug apparent solubility is anticipated in presence of CPV for highly ionized or highly soluble drugs, potentially due to the saturation of the powder surface with excipient particles [50]. In biorelevant media, drug lipophilicity (negative effect, VIP = 1.0) was a significant factor in the model indicating significant reduction in the solubility of highly lipophilic drugs in presence of CPV at 24 hours. The

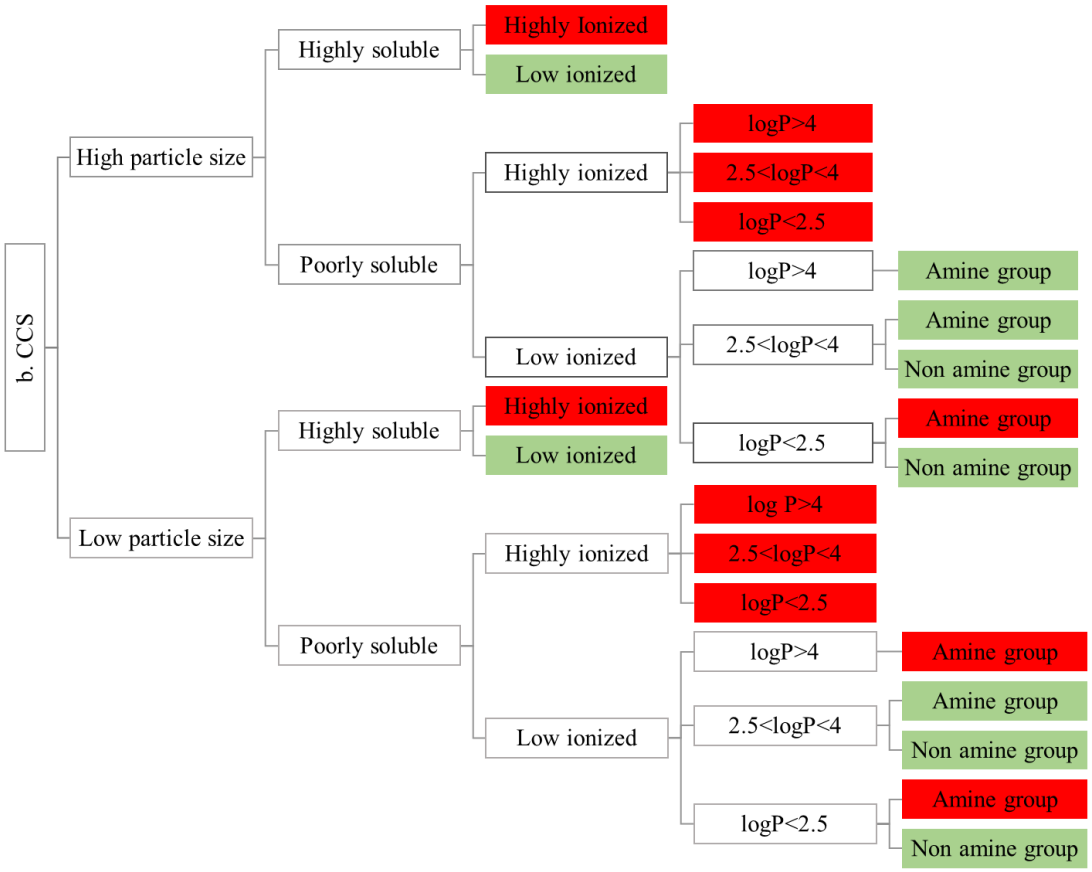
enhanced drug solubilization of lipophilic molecules by the presence of bile salts in biorelevant conditions [47] may result in saturation of the powder surface with excipient particles which further limit drug dissolution and/or drug solubilization. Hydrophobic interactions between lipophilic drugs and CPV [17], could also have contributed to the delay in drug dissolution in excipient presence. Finally, the interaction exc. brand*drug ionization (positive effect, VIP = 1.0) was a significant variable in the biorelevant model but further investigations are needed to explain the nature of this term.

4.3.4. Road map of superdisintegrants effects on drug apparent solubility

The road maps categorizing excipient REs on drug apparent solubility according to excipient (SSG, CCS, CPV) and drug properties are presented in **Figure 4.17** (cases where increased drug solubility was caused by a potential shift in the pH of the medium were not considered).

The impact of the studied superdisintegrants on drug apparent solubility relates to drug physicochemical properties. Presence of low viscosity SSG brands can be critical in oral drug performance for highly ionized drug, irrespective of drug lipophilicity or drug aqueous solubility, as indicated by the pronounced reduction in drug solubility at 24 hours in presence of low viscosity SSG brands (Glycolys LV, Explotab CLV). High viscosity SSG (Glycolys) brands will be challenging for the oral performance of poorly soluble/highly ionized drugs with log P > 4. For poorly soluble/low ionized drugs, presence of SSG is not expected to affect drug solubility, apart from drugs containing a neutral amine group and for which SSG presence may result in significant increase in drug solubility at 24 hours (**Figure 4.17a**).


a. SSG
High viscosity
Low viscosity
Highly soluble
Poorly soluble
Highly soluble
Poorly soluble
Highly Ionized
Low ionized
Highly ionized
Low ionized
Highly ionized
Low ionized
logP>4
2.5<logP<4
logP<2.5
logP>4
2.5<logP<4
logP<2.5
log P>4
2.5<logP<4
logP<2.5
logP>4
2.5<logP<4
logP<2.5
Amine group
Amine group
Non amine group
Amine group
Non amine group
Amine group
Amine group
Non amine group
Amine group
Non amine group


b. CCS
High particle size
Low particle size
Highly soluble
Poorly soluble
Highly soluble
Poorly soluble
Highly Ionized
Low ionized
Highly ionized
Low ionized
Highly ionized
Low ionized
logP>4
2.5<logP<4
logP<2.5
logP>4
2.5<logP<4
logP<2.5
log P>4
2.5<logP<4
logP<2.5
logP>4
2.5<logP<4
logP<2.5
Amine group
Amine group
Non amine group
Amine group
Non amine group
Amine group
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Non amine group
Amine group
Non amine group

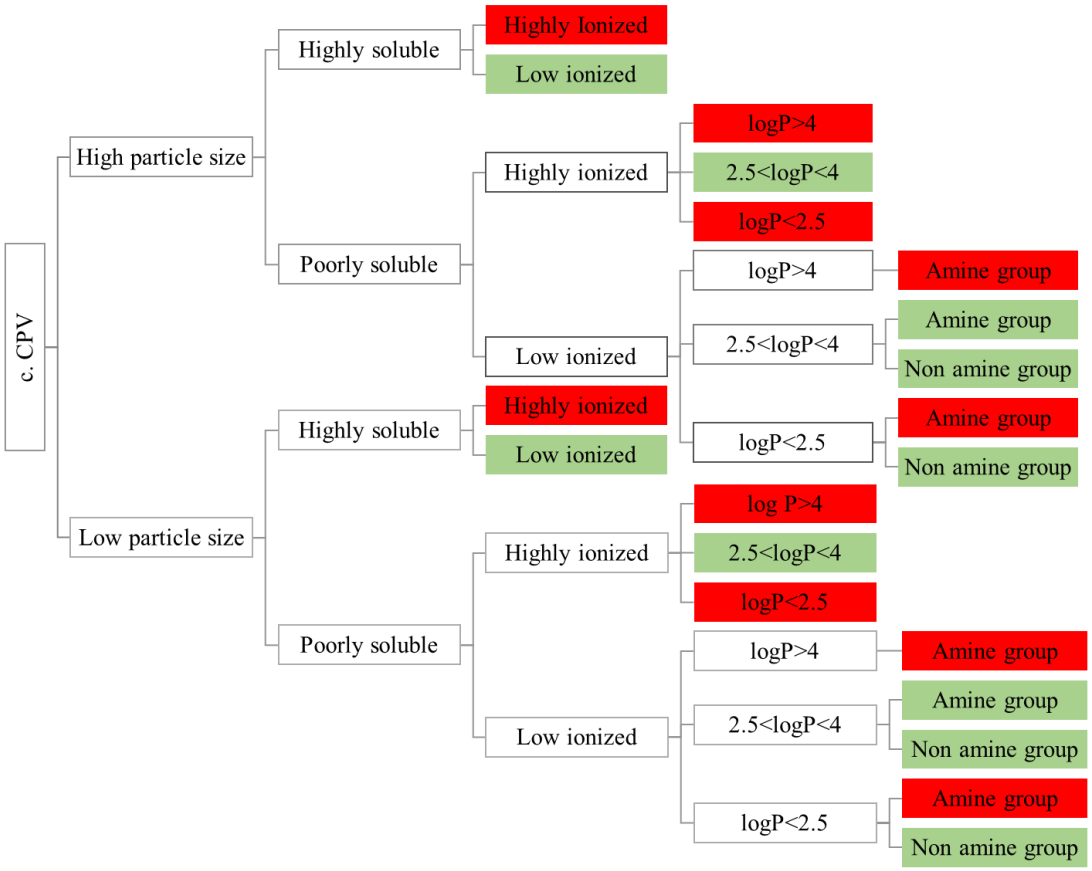

Figure 4.17: Road map of the effects of the studied a. SSG, b. CCS and c. CPV brands on drug solubility. Red boxes and green boxes indicate significant and insignificant changes in drug solubility by excipient presence, respectively.

The criticality of CCS for oral product performance relates to drug ionization as significant changes (decrease) in drug apparent solubility in CCS presence are expected for highly ionized drugs, irrespective of drug aqueous solubility (highly or poorly soluble drugs). Moreover, presence of CCS will be critical for the solubility of poorly soluble/low ionized drugs (log P < 2.5) containing a neutral amine group, as significant increase in the 24 hour drug solubility was observed (**Figure 4.17b**). Presence of low particle size CCS brands may be challenging for the apparent solubility of poorly soluble/low ionized drug with log P > 4, however its impact on drug solubility depends on excipient level (**Figure 4.7**)

The impact of CPV on drug apparent solubility depends on drug ionization and drug lipophilicity, as significant changes (reduction) in the solubility of highly

ionized/highly soluble or highly ionized/poorly soluble drugs with log P < 2.5, irrespective of excipient brand used. Presence of CPV can also be critical for the apparent solubility of highly lipophilic drugs (log P > 4), irrespective of drug ionization state (highly or low ionized), as significant reduction in drug solubility was observed by all the studied CPV brands. Finally, presence of CPV may present challenges in the oral drug performance of poorly soluble/low ionized drugs with log P < 2.5 as significant increase in drug solubility was observed (**Figure 4.17c**).

The construction of roadmaps identified the cases where presence of superdisintegrants can be critical for oral drug performance. Compared to the other two excipient types (lubricants – Chapter 2, binders – Chapter 3), superdisintegrants can be considered as excipients of low criticality for product performance when considering the impact of excipients on drug solubility (the effectiveness of different excipients on tablet disintegration and drug bioavailability also needs to be considered).

4.4. Conclusions

Excipient variability and interchangeability present challenges in pharmaceutical development, as the varying excipient physicochemical properties can affect final product quality. Identification of the critical excipient attributes affecting product performance is recommended for the successful control of excipient variability according to the QbD approach. Presence of superdisintegrants (SSG, CCS, CPV) in immediate release formulations is beneficial for promoting fast tablet disintegration and drug dissolution but there is a lack of knowledge on the impact of their properties on oral drug performance. In this work, the biopharmaceutical implications of superdisintegrant variability on drug apparent solubility were investigated. Solubility studies using compounds with different physicochemical properties revealed that for the majority of cases, presence of superdisintegrants or superdisintegrant variability did not significantly affected drug solubility at 24 hours. The significant changes in drug apparent solubility related to drug physicochemical properties with reduction observed for highly ionized drugs and increased observed for poorly soluble drugs containing a neutral amine group. The use of multivariate data analysis and the design of roadmaps allowed the identification of the biopharmaceutical factors affecting the impact of superdisintegrants on drug apparent solubility. It is concluded that,

compared to other excipient types (lubricants, binders), superdisintegrants can be considered as of low criticality for presenting implications on oral drug absorption (based on drug solubility data).

Acknowledgements

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Chapter 4 Commentary

Superdisintegrants (sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CPV)) constitute an important excipient class for immediate release formulations. This chapter investigated the impact of superdisintegrant presence and variability on drug apparent solubility in a biopharmaceutical perspective. Three brands of SSG of varying viscosity type (Glycolys LV, Explotab CLV, Glycolys) and two brands of CCS (AcDiSol, Primellose) and CPV (Kollidon CL-F, Kollidon CL) of different particle size distribution in two different levels were selected to study the impact of excipient variability and variation on oral drug performance. Presence of superdisintegrants or superdisintegrant variability slightly affected drug solubility at 24 hours for the majority of compounds. Few cases of significant reduction in drug apparent solubility by the studied brands were observed only for highly ionized drugs which were attributed to a drug shielding effect on top of the powder surface by the excipients . Significant increase in drug solubility at 24 hours in presence of SSG, CCS and CPV was observed for poorly soluble drugs containing a neutral amine group and may relate to a drug-excipient interaction or improved powder solubilization in excipient presence. The use of multivariate data analysis revealed that drug physicochemical properties (especially, drug ionization and presence of a neutral amine group) are critical for the impact of superdisintegrants on drug solubility. The data discussed and presented in Chapters 2, 3 and 4 indicate that excipient presence and variability could be critical for oral drug performance however different approaches need to be considered according to the studied excipient class, drug physicochemical properties and/or medium characteristics.

Chapter 5 Preface

The succesful implementation of the Quality by Design (QbD) initiative in pharmaceutical development would be beneficial in the traditional batch or continuous manufacturing leading to the production of robust formulations. Dissolution testing is an important tool in QbD approaches providing information on batch quality, identifying the impact of gastrointestinal conditions on product performance and allowing the development of *in vitro-in vivo* correlations. Traditional (compendial apparatus) or recent advances (surface dissolution UV imaging) on dissolution methods provide mechanistic insights on the role of several components or processes which could affect drug dissolution. Presence of excipients and excipient variability are known to affect drug dissolution both *in vitro* and *in vivo* leading to batch incosistencies, changes in drug bioavailability and bioinequivalence with products. The development of biorelevant dissolution methods to investigate the impact of excipients on drug dissolution would be beneficial towards the understanding and control of excipient variability in the QbD perspective. This would improve the effectiveness of the pharmaceutical manufacturing and would ensure the consistent delivery of safe products for patients. Moreover, the construction of design spaces would allow the minimization of regulatory constraints which are currently strictly addressing the issue of excipient variability. The aim of this chapter is to identify the impact of excipient variability on drug dissolution in a biopharmaceutical perspective. Compendial/biorelevant media and dissolution apparatuses will be used to address the importance of several gastrointestinal conditions on the issue of excipient variability. Assessment of excipient criticality in terms of oral drug performance will be conducted using QbD tools (multivariate data analysis).

Chapter 5. Biopharmaceutical implications of excipient variability on drug dissolution from immediate release products

Abstract

Elucidating the impact of excipient variability on oral product performance in a biopharmaceutical perspective would be beneficial and allow excipient implementation on Quality by Design (QbD) approaches. The current study investigated the impact of varying viscosity of binders (hypromellose (HPMC)) and superdisintegrants (sodium starch glycolate (SSG)) and particle size distribution of lubricants (magnesium stearate (MgSt)) on the *in vitro* dissolution of a highly and a poorly soluble drug from immediate release formulations. Compendial (pharmacopoeia buffers) and biorelevant (media simulating the gastrointestinal fluids) media and the USP 2 and USP 4 apparatuses were used to assess the exerted excipient effects on drug dissolution. Real-time surface dissolution UV imaging provided mechanistic insights into disintegration and dissolution of the immediate release formulations. Varying the viscosity type of HPMC or SSG did not significantly affect drug dissolution irrespective of the compound used. Faster drug dissolution was observed when decreasing the particle size of MgSt brand for the highly soluble drug. The use of real-time surface dissolution UV Imaging revealed the influential role of excipient variability on tablet disintegration, as for the highly soluble drug, tablets containing high viscosity HPMC or low particle size MgSt disintegrated faster (compared to the control tablets) while for the poorly soluble drug, slower tablet disintegration was observed when increasing the viscosity of HPMC (compared to the control tablets). Changes in drug dissolution when varying excipients may be anticipated if the excipient change has previously affected drug solubility. The use of multivariate data analysis revealed the influential biopharmaceutical factors (critical excipient types/properties, drug aqueous solubility, medium/hydrodynamic characteristics) affecting the impact of excipients on *in vitro* drug dissolution.

Keywords: excipient variability, HPMC, sodium starch glycolate, magnesium stearate, *in vitro* drug dissolution, multivariate data analysis

5.1. Introduction

Introduction of the Quality by Design (QbD) initiative in the pharmaceutical industry is crucial for the development of robust manufacturing processes and the safety of final products. The requirements of a final dosage form are identified from a patient perspective and are translated into critical quality attributes (CQAs). Critical material attributes (CMAs) of input raw materials and critical process parameters (CPPs) for the manufacture of dosage forms must then be controlled to ensure that the CQAs are delivered [1]. Control strategies and design spaces are built to cope with the variability and/or variation of the factors affecting product manufacturing or performance [2]. Implementation of QbD approaches in the traditional pharmaceutical development can prevent batch failures and improve cost effectiveness due to the scientific understanding and control of the manufacturing processes [1]. The principles of QbD could, as well, be beneficial in emerging technologies, such as continuous manufacturing, as they will allow the identification, control and monitoring of the continuous dynamic processes during development [3].

Dissolution testing can be a powerful tool in the QbD concept providing information on the critical factors that can affect oral drug absorption [4]. Quality control dissolution methods can assess inter-batch consistencies, as they are developed to discriminate the critical factors (CMAs or CPPs) affecting the performance of final dosage forms [5]. The development of biorelevant dissolution methods demonstrates the ability of dissolution testing to delineate the impact of physiological conditions (pH of the medium, presence of solubilizing components, fasted vs fed state, hydrodynamics) on product performance [6]. Prediction of the in vivo product performance through dissolution tests (clinically relevant dissolution methods) can be achieved with the development of *In vitro-In vivo* correlations (IVIVC) that will assist in the identification of CQAs and substitute in vivo bioequivalence studies [7]. Media (compendial: pharmacopeia buffers, biorelevant: mimicking the composition of the gastrointestinal fluids) [8, 9] and apparatus (USP 1: basket assembly, USP2: paddle assembly, USP 3: reciprocating cylinder, USP 4: flow-through cell) [10] able to simulate gastrointestinal conditions and predict oral product performance have been developed to serve the purposes of the dissolution methods. Moreover, recent advances in real-time surface dissolution UV-imaging techniques have allowed the spatial and temporal visualization of the dissolution phenomena of APIs from

compacts [11-13] or dosage forms [14], the role of excipients [15-17] and physiological conditions (pH [18, 19], hydrodynamics [15], biorelevant media [20]) on drug dissolution. These techniques could provide additional information on the mechanisms by critical factors can affect *in vitro* drug dissolution.

The critical role of excipient presence, variability (changes in material properties) or variation (changes in amount) on product quality is highlighted [21, 22] and it is recognized that the effects of excipients on product performance relate to several biopharmaceutical factors (gastrointestinal conditions, drug physicochemical properties) [23]. Several studies have shown that changes in the physical or chemical excipient composition, changes in the amount of excipient used and excipient interchangeability affected *in vitro* drug dissolution [23]. Increasing the viscosity type of cellulosic polymers (hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC)) resulted in slower theophylline release from hydrophilic matrix tablets (USP2 apparatus, 900 mL distilled water, 37 °C, 50 rpm and 100 rpm for tablets containing HPC and HPMC, respectively) [24, 25]. Pronounced delay in the dissolution and release of theophylline from matrix tablets (USP1 apparatus, distilled water, 37 °C, 100 rpm) containing magnesium stearate (MgSt) was observed with increasing excipient level (1% w/w – 5% w/w) [26]. The dissolution profiles of hydrochlorothiazide from tablets containing crospovidone brands from two different suppliers (USP1 apparatus, 900 mL 0.1 N HCl pH 1, 37 °C, 100 rpm) were not similar due to the differences in excipient porosity, despite the interchangeability of the studied brands [27, 28]. The implications of excipients on in vivo product performance have been highlighted, as changes in drug bioavailability and bioinequivalence within products have been attributed to excipient presence [29]. Bioequivalence studies failed to show similarity between innovator and generic products of alendronate, as the presence of sodium lauryl sulfate in the generic product resulted in a 5-fold increase in drug bioavailability [29]. International associations and regulatory agencies are strictly addressing the issue of excipient variability on product performance. Evaluation of the significance of excipient changes [30] and excipient functionality [31, 32] on drug dissolution is needed. Scientific justification that excipient changes will not affect formulation quality and performance is required by regulatory agencies [33]. Scale-up or post approval excipient changes may or may not require *in vitro* dissolution documentation according to excipient type or amount and

drug characteristics (Level 1: deletion of colouring/flavouring agents or changes in excipient amount within specified limits do not require additional dissolution documentation, Level 2: changes in excipient technical grades or excipient amount greater than the Level 1 limits require addition dissolution justification). Failure to meet *in vitro* dissolution criteria requires full dissolution and bioequivalence documentation (Level 3) [33]. Excipient changes when requesting biowaivers are also considered as excipients may affect drug absorption and it is recommended that test products contain qualitatively the same and quantitatively very similar excipients [34, 35].

The aim of this study was to identify the impact of excipient variability on *in vitro* drug dissolution in a biopharmaceutical perspective. Excipient variability was assessed by obtaining variants in critical material attributes of binders (hypromellose (HPMC) – viscosity type), superdisintegrants (sodium starch glycolate (SSG) – viscosity type) and lubricants (magnesium stearate (MgSt) – particle size distribution (PSD)) and producing immediate release formulations (control and variant tablets) for a highly and a poorly soluble model compound using wet granulation. Dissolution studies were performed in compendial and biorelevant media with the USP 2 and USP 4 apparatus. Real-time surface dissolution UV imaging was also performed to provide a mechanistic understanding of the dissolution processes of the manufactured tablets. Multivariate data analysis (Partial Least Squares (PLS)) was used to understand the effects of certain variables (excipient critical material attributes, drug aqueous solubility, medium and hydrodynamic characteristics) on the impact of excipients on drug dissolution.

5.2. Materials and Methods

5.2.1. Materials

APIs: Paracetamol and carbamazepine were kindly donated by AstraZeneca. Excipients: Mannitol (Pearlitol 160C, Roquette Frères, France), microcrystalline cellulose (Avicel PH101, FMC Biopolymer, USA), hypromellose (HPMC) (Methocel E5 and Methocel E15, Dow Chemical Company, USA), sodium starch glycolate (SSG) (Glycolys and Glycolys LV, Roquette Frères, France), magnesium stearate (MgSt) (Ligamed MF-2-V and Ligamed MF-3-V, Peter Greven, Netherlands) were purchased by the specified sources. Chemicals: Hydrochloric acid 36.5–38%, HPLC

grade methanol, pepsin (from porcine) were obtained from Sigma-Aldrich (UK). Maleic acid, sodium chloride, sodium hydroxide, potassium phosphate monobasic were obtained from Fisher Scientific (UK). Sodium taurocholate (Prodotti Chimici Alimentari S.P.A., Italy), egg lecithin – Lipoid EPCS (Lipoid GmbH, Germany), were obtained from the sources specified. Water was ultra-pure (Milli-Q) laboratory grade. Filters: Cronus 13 mm regenerated cellulose (RC) syringe filters 0.45 μm were purchased from LabHut (UK), Whatman® 24 mm glass fibre filters 0.7 μm pore size (GF/F) and Whatman® 24 mm glass microfibre filters 2.1 μm pore size (GF/D) were purchased from Fischer Scientific (UK). Glass wool was obtained from Sigma Aldrich (UK).

5.2.2. Instrumentation

Equipment used included: a Pharmatech drum blender (Pharmatech, UK), a Consigma^{TM}-1 granulator (GEA Pharma Systems, Belgium), a Quadro Comill 193 (Ytron Quadro Ltd, UK) equipped with a 1397 μm screen, a turbula blender Type T2F (GlenMills Inc., USA), a Kilian Styl'One Evo press (Romaco Kilian, Germany) equipped with 11 mm normal ankle cave punches, a Mettler Toledo SR32001 DeltaRange balance (Mettler Toledo, Switzerland), digital calipers (Mitutoyo Ltd, UK), a Sotax HT100 automated tablet tester (Sotax, Switzerland), a Erweka ZT70 disintegration tester (Erweka GmbH, Germany), a VK-7000 Vankel® USP 2 apparatus (Vankel® dissolution system, USA) connected with an VK-750D external heating circulator (Vankel®, USA), a DFZ720 Erweka® flow-through dissolution tester connected to a HKP 720 Erweka® piston pump (Erweka GmbH, Germany), an SDi2 surface dissolution UV imaging system (Pion Inc., USA), a UV-Vis spectrophotometer (Ocean Optics, USA), a Buchi R114 Rotavapor (Buchi, Switzerland), a Mettler Toledo SevenCompact S210 pH meter (Mettler Toledo, Switzerland), an Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A), autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector (G1329A) and a Chemstation software (Agilent Technologies, USA),

5.2.3. Methods

5.2.3.1. Tablet manufacturing

Granules containing drug, mannitol, microcrystalline cellulose, HPMC, SSG (Table 5.1) were prepared by twin screw granulation. Drug and excipients were mixed for 30 minutes at 25 rpm. Wet granulation was performed using distilled water as the granulation liquid, with a screw speed at 900 rpm, powder mass flow at 15 kg/h and liquid mass flow at 100 g/min. Granules were collected and left to dry overnight at 60 °C (at a drying end point of < 2% moisture loss on drying). Granules were milled at 2000 rpm with a 1.4 mm mesh to improve granule flow and filling in the die for compression. Granules were lubricated with MgSt for 3 minutes with a speed of 30 rpm. Tablets were manufactured at a compression force of 20 kN for PRC and 15 kN for CBZ. 200 tablets for each of the PRC or CBZ batches (control and variant tablets) were produced.

5.2.3.2. Tablet characterization

The manufactured tablets were characterized in terms of tablet mass, thickness, width, hardness and disintegration time. Tablet mass was measured using an analytical balance. Tablet thickness and width were measured using digital callipers. Tablets hardness was assessed using an automated tablet tester. 10 tablets from each PRC and CBZ batches (control and variant tablets) were used to calculate the mean tablet mass (mg) ± standard deviation (SD), mean tablet thickness (mm) ±SD, mean tablet width (mm) ±SD and mean tablet hardness (N) ±SD. Tablet disintegration time was measured with the basket method at 37°C using distilled water as the immersion fluid [36]. The disintegration time (time at which tablet particles passed through the mesh at the bottom of the basket) was automatically recorded. The mean disintegration time (min) ±SD for 6 PRC and 3 CBZ tablets (for each control and variant tablets) was determined.

5.2.3.3. Media used for dissolution studies

Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to the method described in the United States Pharmacopeia [37]. Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF-V2) were prepared as previously described [38].

Table 5.1: Composition of the manufactured tablets

	% w/w	Control Batch	HPMC Variant	SSG Variant	MgSt Variant
PRC/CBZ	25	TBC/Fagron	TBC/Fagron	TBC/Fagron	TBC/Fagron
Mannitol	34	Pearlitol 160C	Pearlitol 160C	Pearlitol 160C	Pearlitol 160C
Microcrystalline cellulose	34	Avicel PH101	Avicel PH101	Avicel PH101	Avicel PH101
HPMC	3	Methocel E5 (low viscosity)	**Methocel E15 (high viscosity)**	Methocel E5 (low viscosity)	Methocel E5 (low viscosity)
SSG	4	Glycolys (high viscosity)	Glycolys (high viscosity)	**Glycolys LV (low viscosity)**	Glycolys (high viscosity)
Extragranular MgSt	2	Ligamed MF-2-V (high PSD*)	Ligamed MF-2-V (high PSD)	Ligamed MF-2-V (high PSD)	**Ligamed MF-3-V (low PSD)**

*PSD = particle size distribution

5.2.3.4. *In vitro* dissolution studies

5.2.3.4.1. USP 2 apparatus

Experiments were performed at 37 °C using 500 mL of dissolution medium (compendial or biorelevant). The rotational speed of the paddle was set at 50 rpm. 3 mL samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 min for PRC and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240 min for CBZ, filtered through RC 0.45 μm pore size filters, diluted with the corresponding medium (if needed) and analysed by HPLC. Filter adsorption studies were prior performed in triplicate for each drug and confirmed no adsorption issues for the studied drugs on the filters used. At each sampling time point the volume of the withdrawn samples was replaced with fresh corresponding dissolution medium. All experiments were performed in triplicate.

5.2.3.4.2. USP 4 apparatus

Experiments were performed at 37 °C using the Ø 12 mm (small) and Ø 22.4 mm (large) cells for PRC and the Ø 12 mm (small) cells for CBZ. A 5 mm-size ruby bead was positioned in the tip of the cell and 1g (small cells) or 6g (large cells) of 1 mm-sized glass beads were added. On the top of the cell a GF/F filter was placed for PRC and one GF/F filter, 0.15 g of glass wool and one GF/D filter were placed for CBZ. The flow rate was set at 4 mL/min. For PRC the closed-loop configuration was used. 3 mL samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 min, diluted with the corresponding medium and analysed by HPLC. At each sampling time points the volume of the withdrawn samples was replaced with fresh corresponding dissolution medium. For CBZ the open-loop configuration was used. Dissolution samples were collected in a volumetric cylinder, samples were diluted with the corresponding medium and analysed by HPLC. Cylinders were exchanged at 5, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 240 min after the beginning of the experiment. All experiments were performed in triplicate.

5.2.3.5. Real – time surface dissolution UV imaging

Surface dissolution UV imaging was performed using the SDi2 instrument with a USP 4 type flow-cell (cell volume: 60.3 mL, cell diameter: 28 mm, effective imaging area: 28 x 24 mm^2). Dissolution studies of the PRC and CBZ tablets (control and variant tablets) were conducted at a flow rate of 6.16 mL at 37 °C using 0.1 N HCl pH

1 as dissolution medium for 20 minutes. This flow rate was selected to simulate the linear velocity (1 cm/min) in the USP 4 (large cells) when operating at 4 mL/min. Dual-wavelength imaging was performed using two Light Emitting Diodes (LEDs) at 300 and 520 nm for PRC and 320 and 520 nm for CBZ. Drug quantification was also assessed by monitoring drug concentrations of the effluent at 1 minute intervals using a photodiode array UV-Vis spectrophotometer and used for the construction of the dissolution profiles. Drug quantification in the effluent was made based on calibration curves (calibration ranges: 2 – 50 μg/mL for PRC, 20 – 150 μg/mL for CBZ). Real-time surface dissolution UV images showing the disintegration and dissolution phenomena of the studied tablets were obtained and processed using the SDi2 analysis software v. 3.0.22 (Pion Inc, USA). All experiments were performed in triplicate.

5.2.3.6. Chromatographic conditions

Drug quantification in the dissolution samples was performed by HPLC-UV. Analytical HPLC procedures were modifications of already published methods for PRC [39] and CBZ [40]. A reversed-phase Spherisorb (Waters) C18 column (250 × 4.6 mm, 5 μm) was used for both drugs. For PRC, the mobile phase consisted of methanol and water 20:80 (v/v) and the temperature was kept constant at 20 °C. The injection volume was 20 μL and the detection wavelength was at 257 nm. For CBZ, the mobile phase was composed of methanol and water 60:40 (v/v) and the temperature was kept constant at 25 °C. The injection volume was 100 μL and the detection wavelength was at 285 nm. The flow rate was set at 1 mL/min for both drugs (isocratic flow). The elution times were 6 min and 4 min for PRC and CBZ, respectively. Drug quantification was made based on calibration curves. Standards were formulated from concentrated stock solution of drug dissolved in MeOH (PRC: 2 mg/mL, CBZ: 1 mg/mL). The range of the calibration curves were 10 – 200 μg/mL and 10 -150 μg/mL for PRC and CBZ, respectively.

5.2.3.7. Treatment of *in vitro* dissolution data

The cumulative % of drug dissolved in the USP 2 apparatus and USP 4 apparatus – closed loop configuration was calculated based on drug quantification from the analytical method (HPLC) and the amount of drug in the manufactured tablets. The cumulative % of drug dissolved in the USP 4 apparatus - open loop configuration and the effluent analysis of the SDi2 was calculated based on drug quantification from the

analytical method (HPLC for the samples obtained with the USP 4 apparatus, spectroscopy for the samples obtained with the SDi2), the flow rate of the system and the amount of drug in the manufactured tablets. The dissolution profiles depicting the cumulative % of drug dissolved from the control and variant tablets as a function of time were generated using Spotfire 7.10.1 (TIBCO software Inc, USA). The area under the curve (AUC) of the dissolution profiles, calculated using the method of trapezoids, was used for the characterization of drug dissolution. In cases where the dissolution profiles reached a plateau level, the AUC of the dissolution profiles was calculated up to the time corresponding to the first experimental datum after the 85% of drug dissolution for both the control and variant tablets in each medium [41]. In cases where the dissolution profiles did not reach a plateau level, the AUC of the dissolution profiles was calculated up to the last experimental time point. The Relative Effect (RE_{AUC}) of each excipient variant on the AUCs of the dissolution profiles was calculated based on Equation 5.1:

$$RE_{AUC} = \frac{(AUC_T - AUC_R)}{AUC_R} x\ 100 \qquad \text{equation 5.1}$$

where AUC_R and AUC_T are the areas under the curve of the dissolution profiles of the reference and test product, respectively. Two sets of comparisons were performed. In the first set (set 1), the differences in drug dissolution within the studied tablets in each medium were examined taking the AUCs of the dissolution profiles of the control and variant tablets as reference and test dissolution profiles, respectively. In the second set (set 2), differences in drug dissolution within acidic and basic conditions (in compendial and biorelevant media) for each tablet batch were investigated taking the AUCs of the dissolution profiles in acidic and basic conditions as the reference and test dissolution profiles, respectively. Dissolution performance in presence of excipients was correlated to the drug apparent solubility in excipient presence using the REs of excipients on AUCs of the dissolution profiles and the relative increase or decrease in drug solubility by the studied excipients ; the solubility data of PRC and CBZ (presented in chapters 2, 3 and 4) in presence of 2% HPMC, 5% SSG or 2% MgSt were used. The Relative Effect (RE_S) of each excipient on drug solubility were calculated based on Equation 5.2:

$$RE_S = \frac{(S - Sr)}{Sr} x\ 100 \qquad \text{Equation 5.2}$$

where S and Sr denote drug solubility in presence of the excipient brand of the variant tablets and in presence of the corresponding excipient brand in the control tablets. The risk assessment of the impact of excipients on drug dissolution or drug solubility was evaluated by setting reference range criteria of -20% - 25% [42] on the RES_{AUC} or RES_S (this range was selected as a similar range is set in order to assess differences in drug exposure after oral administration; i.e. in bioequivalence studies). RES_{AUC} or RES_S outside these values (RE_{AUC} or RES_S < -20% or RE_{AUC} or RES_S > 25%) were considered critical for oral drug performance.

5.2.3.8. Statistical analysis of *in vitro* dissolution data

5.2.3.8.1. *In vitro* dissolution profile comparisons

Dissolution profile comparisons were performed with the use of the f_2 (similarity factor) assuming the dissolution profiles of the control and variant batches as the reference and test dissolution profiles, respectively, according to Equation 5.3:

$$f2 = 50\, x \log\{ [1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5}\, x\, 100\} \qquad \text{equation 5.3 [41]}$$

where Rt and Tt are the reference and test % cumulative profiles at time t, respectively and n is the number of sampling points. Evaluation of f_2 was considered up to the time corresponding to the first experimental datum after the 85% of drug dissolution of both the control and variant tablets in each medium [41]. In cases where 85% of drug dissolution was not reached at the end of the experiment, dissolution profile comparisons were performed up to the last experimental time point. Mean data sets were used as the coefficient of variation was less than 20% and 10% for early (up to 15 min) and late time points, respectively. Differences between the dissolution profiles of the test from the reference product were identified setting a 10% difference (f_2 < 50).

5.2.3.8.2. Multivariate data analysis of *in vitro* dissolution data

Excipient REs on drug dissolution were correlated to excipient critical material attributes (viscosity for HPMC and SSG, PSD for MgSt), drug aqueous solubility ($Drug_{aq.sol.}$), medium properties (gastric, intestinal) and hydrodynamics (USP apparatus) by partial least squares (PLS) regression using the XLSTAT software (Microsoft, USA). Two models for the REs of excipients on the AUCs of the

dissolution profiles in compendial media (Model 1) and biorelevant media (Model 2) were constructed. The evaluated variables for both models were all categorical and are presented in **Table 5.2**. Excipient REs on the AUCs of the dissolution profiles (set 1, section 2.2.6.) were used as the response. The selected interaction terms included each excipient variant combined with each drug aqueous solubility ($Drug_{aq.sol.}$), medium property (gastric, intestinal) and hydrodynamic characteristics (USP apparatus). The generated PLS models were assessed in terms of goodness of fit (R^2) and goodness of prediction (Q^2). High values of R^2 and Q^2 with a difference not greater than 0.2 - 0.3 were indications of successful models [43]. The number of PLS components (lines on the X-space which best approximate and correlate with the Y-vector) was based on minimum predictive residual sum of squares (PRESS) [43]. From the available components the one at which Q^2 reached its maximum value was selected [44]. Standardized coefficients were used to show the direction (positive or negative) and extent of each variable on the response. The significance of the variables was assessed by the variable influence on projection (VIP) value. The significance of the variables was assessed by the variable influence on projection (VIP) value. VIP values > 0.8 were considered as moderately influential in the model while VIP values > 1 were considered the most influential in the model [43]. A 95 % confidence interval was used.

Table 5.2: Parameters evaluated with multivariate statistical analysis

Parameter	**Level**	
	0	**1**
$Drug_{(aq.sol.)}$*	Poorly soluble	Highly soluble
Medium	Gastric	Intestinal
Hydrodynamics	USP 2 apparatus	USP 4 apparatus
USP 4 hydrodynamics	Small cells	Large cells
HPMC variant	HPMC – control tablets	HPMC – variant tablets
SSG variant	SSG – control tablets	SSG – variant tablets
MgSt variant	MgSt – control tablets	MgSt – variant tablets

* $Drug_{(aq.sol)}$ = Drug aqueous solubility

5.3. Results and Discussions

5.3.1. Tablet characterization

The properties of the manufactured PRC and CBZ tablets are presented in **Table 5.3**. Tablets of approximately 500 mg mass, 5.5 mm thickness and 11.0 mm diameter were produced irrespective of model compound or variant used. Comparison of the control tablets of PRC and CBZ showed lower hardness and faster disintegration time for the CBZ control tablets which could be explained by the lipophilic nature of CBZ (log P = 2.45, source DrugBank). For PRC, the HPMC variant tablets (high HPMC viscosity) exhibited lower hardness and faster disintegration compared to the control tablets (low HPMC viscosity), as densification of HPMC reduces with increasing excipient viscosity [45]. For CBZ, the tablet hardness of the control and the HPMC variant tablets were similar. The slower disintegration of the HPMC variant tablets compared to the control tablets may be explained by the higher viscosity of the HPMC variant [46]. The SSG variant tablets (low SSG viscosity) were softer compared to the control tablets (high SSG viscosity) in the case of PRC. As higher degree of crosslinking between the hydroxyl groups of SSG reduces the solubility of the polymer [47, 48] the lower tablet hardness may be attributed to the decreased polymer hydrophilicity or the formation of less hydrogen bonds in the SSG variant compared to the control tablets. Differences in tablet hardness between the control and SSG variant tablets were not observed for CBZ. Highly crosslinked SSG brands (low SSG viscosity) would be expected to lead to faster tablet disintegration due to the increased water uptake [49], however, differences in tablet disintegration between the SSG variant and control tablets were minor irrespective of model compound. The presence of 2% of MgSt may have affected the penetration rate of water into tablets and diminish the differences in disintegration time between the studied SSG brands [47]. The MgSt variant (low MgSt particle size) produced softer tablets compared to the control tablets (high MgSt particle size) for PRC as a result of the better lubrication efficiency of the lower particle size of the MgSt variant [50]. The faster disintegration of the MgSt variant tablets compared to the control tablets is attributed to its lower tablet hardness [51]. No impact on the hardness and disintegration data were found when varying MgSt brand for CBZ

Table 5.3: Properties of the manufactured tablets (n =10, Mean ± SD. For disintegration time PRC: n = 6, Mean ± SD, CBZ: n = 3, Mean ± SD)

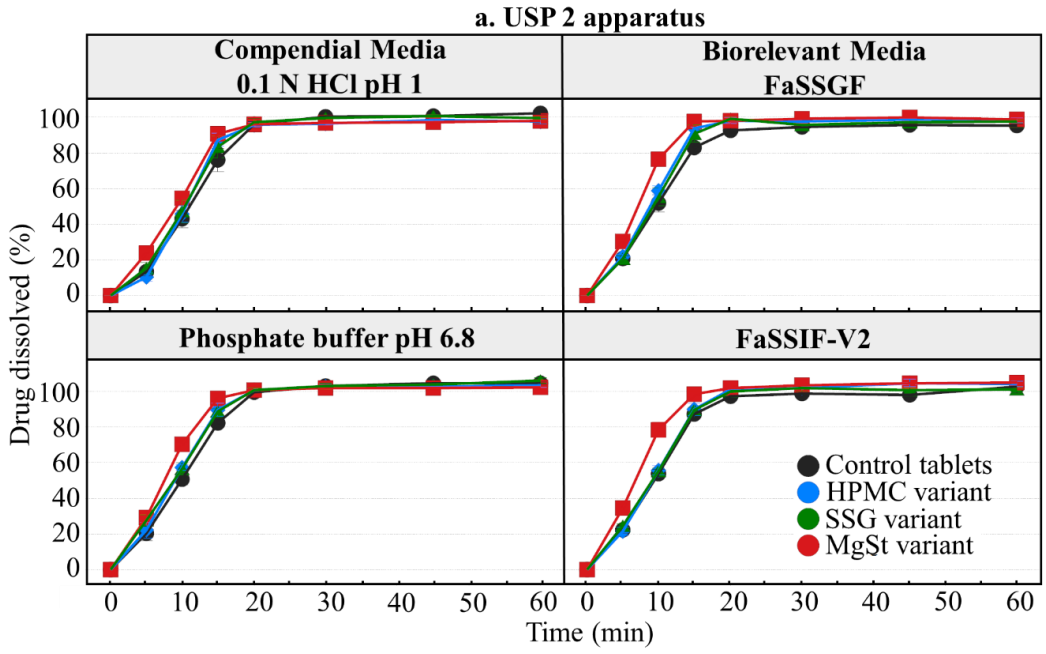
	Mass (mg)		**Width (mm)**		**Thickness (mm)**		**Hardness (N)**		**Disintegration time (min)**	
	PRC	CBZ	PRC	CBZ	PRC	CBZ	PRC	CBZ	PRC	CBZ
Control tablets	506.40 (± 2.39)	506.04 (± 5.94)	11.01 (± 0.00)	11.11 (± 0.03)	5.26 (± 0.01)	5.50 (± 0.03)	242.30 (± 8.22)	145.90 (± 5.30)	10:27 (± 0.01)	08:09 (± 0.03)
HPMC Variant	501.52 (± 3.00)	509.74 (± 2.96)	11.05 (± 0.00)	11.05 (± 0.02)	5.26 (± 0.02)	5.40 (± 0.03)	195.90 (± 5.05)	139.30 (± 5.59)	08:20 (± 0.01)	11:43 (± 0.03)
SSG Variant	514.68 (± 2.82)	496.49 (± 3.50)	11.04 (± 0.00)	11.05 (± 0.01)	5.35 (± 0.02)	5.30 (± 0.03)	187.30 (± 5.68)	148.70 (± 3.91)	11:07 (± 0.02)	08:19 (± 0.00)
MgSt Variant	522.36 (± 3.58)	508.63 (± 2.85)	11.05 (± 0.00)	11.07 (± 0.02)	5.49 (± 0.03)	5.39 (± 0.02)	149.20 (± 10.86)	141.90 (± 6.91)	07:59 (± 0.02)	08:16 (± 0.01)

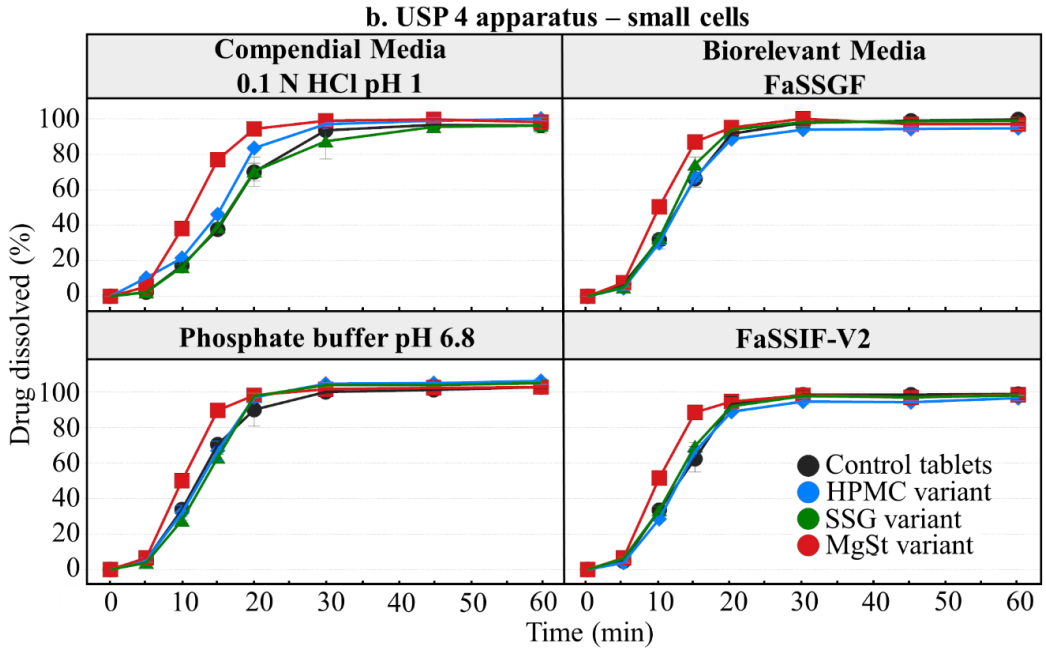
5.3.2. *In vitro* dissolution studies

5.3.2.1. Control Tablets

5.3.2.1.1. Highly soluble drug (PRC)

The dissolution profiles of PRC from the control and variant tablets in compendial and biorelevant media in the USP 2, USP 4 (small cells) and USP 4 (large cells) apparatuses are presented in **Figure 5.1**.





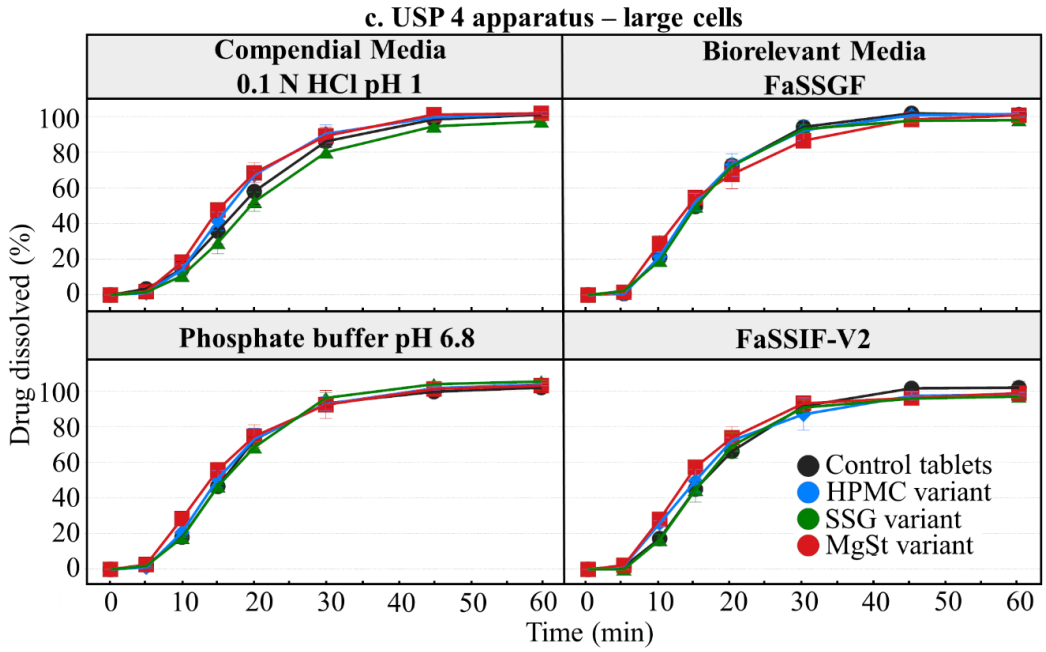


Figure 5.1: Cumulative % dissolved of PRC from tablet formulations in compendial and biorelevant media using the a. USP 2 apparatus (500 mL, 50 rpm, 37°C), b. USP 4 apparatus (closed mode, small cells, 500 mL, 4 mL/min, 37°C) and c. USP 4 apparatus (closed mode, large cells, 500 mL, 4 mL/min, 37°C). The different tablets are shown as: i. control tablets (black circles), ii. HPMC variant tablets (blue diamonds), iii. SSG variant tablets (green triangles) and iv. MgSt variant tablets (red squares). (Mean ± SD, n = 3)

The dissolution of PRC from the control tablets was complete in all experimental conditions. In the USP 2 apparatus, the 85% of drug dissolution was reached in 20 min in 0.1 N HCl pH 1, phosphate buffer pH 6.8 and FaSSGF and in 15 min in FaSSIF-V2. The faster drug dissolution in FaSSIF-V2 can be explained by the presence of bile salts improving tablet wetting [8]. In the USP 4 apparatus, the 85% of drug dissolution from the control tablets was reached in 30 min in 0.1 N HCl pH 1 and in 20 min in phosphate buffer pH 6.8, FaSSGF and FaSSIF-V2 when the small cells were used and in 30 min in all experimental conditions when the large cells were used. The applied hydrodynamics differ between the two studied systems as turbulent flows prevail in the USP 2 apparatus [52] while laminar flows exist in the USP 4 apparatus when glass beads are used [53]. Comparison of the hydrodynamics between apparatuses is

conducted with the use of Reynolds number (ratio of inertial to viscous forces in the fluid) which relates to the fluid and linear velocities in the studied apparatuses and associates with the mass transfer rates [54]. High fluid velocities (corresponding to high Reynolds number) have been reported in the USP 2 apparatus (fluid velocity of 0.049 m/s from the top surface of the tablet [10]) while the laminar flows in the USP 4 apparatus results in low fluid velocities (low Reynolds numbers) (small cells: 0.005 m/s, large cells: 0.001 m/s [54]). In the USP 4 apparatus, the lower linear velocities at equivalent flow rates in the large compared to the small cells relate to the increased cross-sectional area of the large cells [55]. Therefore, the slower drug dissolution in the USP 4 (small and large cells) compared to the USP 2 apparatus and in the USP 4 apparatus (large cells compared to the small cells) is justified by the differences in fluid velocities within the studied apparatuses. The REs of excipients on the AUCs of the dissolution profiles between acidic and basic conditions in compendial and biorelevant media are presented in **Figure 5.2**. The positive RE_{AUC} in compendial media indicate more complete drug dissolution in basic compared to acidic conditions. Presence of SSG or MgSt may lead to slower dissolution in acidic compared to basic conditions due to the reduced liquid water uptake by the neutral form of SSG [56] or the slower dissolution of stearic acid (dissociation product of MgSt) which limits drug dissolution [57] in acidic media. Differences in the RE_{AUC} of excipients between acidic and basic media are less pronounced in biorelevant media, as the presence of the solubilizing components in these media facilitates tablet wetting and enhances drug dissolution [58].

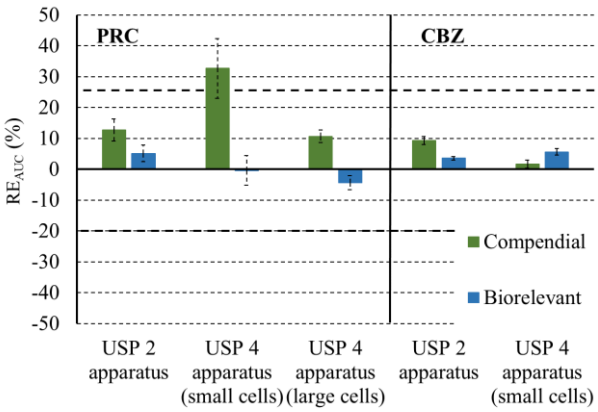


Figure 5.2: Relative effects of excipients on the AUCs of the dissolution profiles between acidic and basic conditions for PRC and CBZ from the control tablets in compendial (green colour) and biorelevant (blue colour) media. (Mean ± SD, n = 3)

5.3.2.1.2. Poorly soluble drug (CBZ)

The dissolution profiles of CBZ from the control tablets in compendial and biorelevant media in the USP 2 and USP 4 (small cells) apparatuses are presented in **Figure 5.3**.

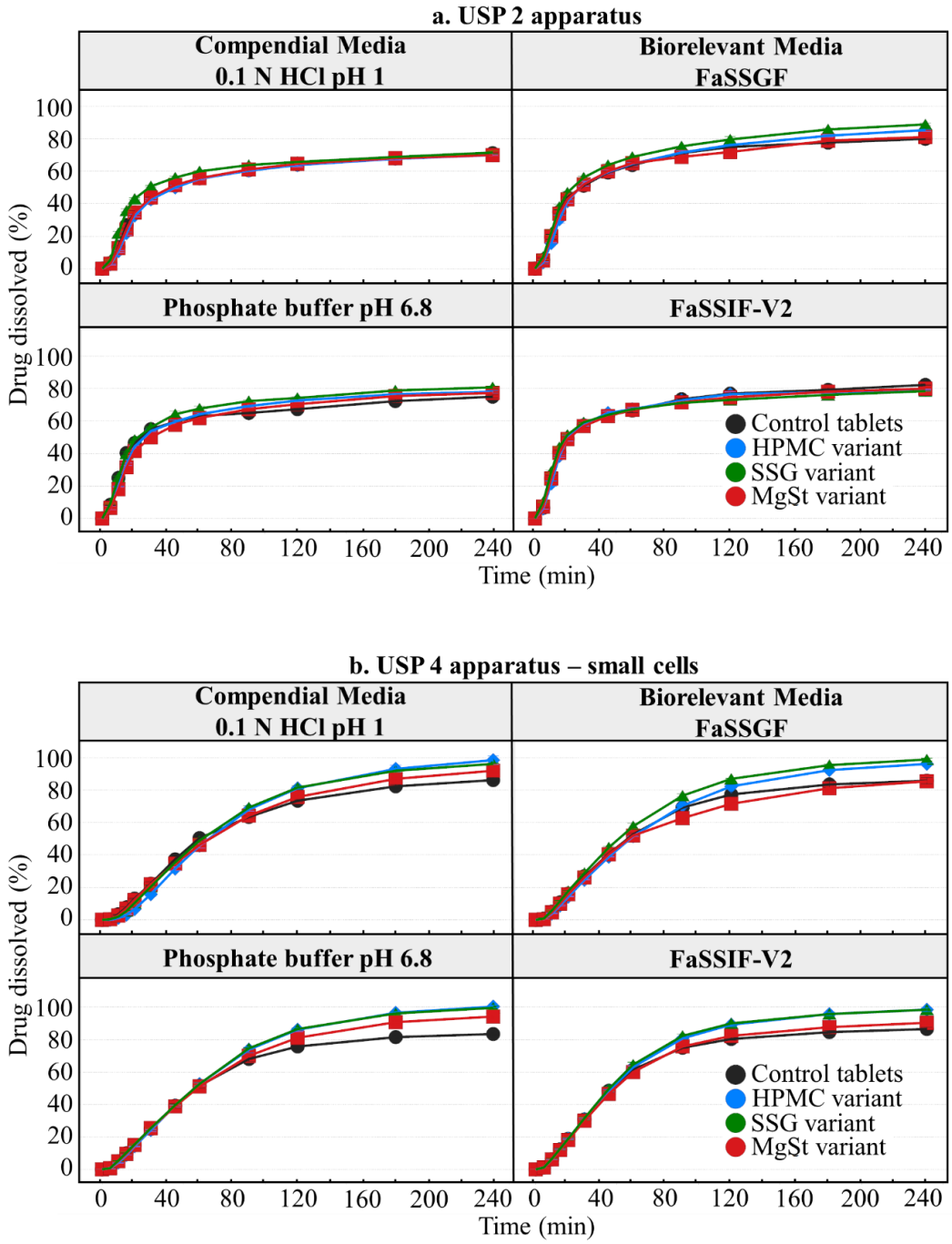


Figure 5.3: Cumulative % dissolved of CBZ from tablet formulations in compendial and biorelevant media using the a. USP 2 apparatus (500 mL, 50 rpm, 37°C) and b. USP 4 apparatus (open mode, small cells, 4 mL/min, 37°C). The different batches are

shown as: i. control tablets (black circles, ii. HPMC variant tablets (blue diamonds), iii. SSG variant tablets (green triangles) and iv. MgSt variant tablets (red squares). (Mean ± SD, n = 3)

In the USP 2 apparatus, the dissolution of CBZ in the studied media was not complete (70% - 80% of drug dissolved at 4 hours), due to the lack of sink conditions. In the USP 4 apparatus, approximately 85% of drug dissolution was reached after 4 hours from the control batch as sink conditions were achieved due to the open-loop configuration [53]. The REs of excipients on the AUCs of the dissolution profiles between acidic and basic conditions revealed slightly more complete drug dissolution in basic conditions ($2\% < RES_{AUC} < 10\%$) in the studied conditions (**Figure 5.2**). This indicates that the pH dependent performance of certain excipients (SSG or MgSt) will be less pronounced for poorly soluble drugs.

5.3.2.2. HPMC variant

5.3.2.2.1. Highly soluble drug (PRC)

Complete drug dissolution from the HPMC variant tablets was observed in the studied experimental conditions (**Figure 5.1**). In the USP 2 apparatus, the 85% of drug dissolution from the HPMC variant tablets was reached faster compared to the control tablets in 0.1 N HCl pH 1, phosphate buffer pH 6.8 and FaSSGF (15 min vs 20 min for the HPMC variant tablets and control tablets, respectively). Differences in the time to reach 85% of drug dissolution between the HPMC variant tablets and the control tablets were not observed in FaSSIF-V2 in the USP 2 apparatus and in all experimental conditions in the USP 4 apparatus (small and large cells). The REs of excipients on the AUCs of the dissolution profiles between the HPMC variant tablets and the control tablets are presented in **Figure 5.4a**.

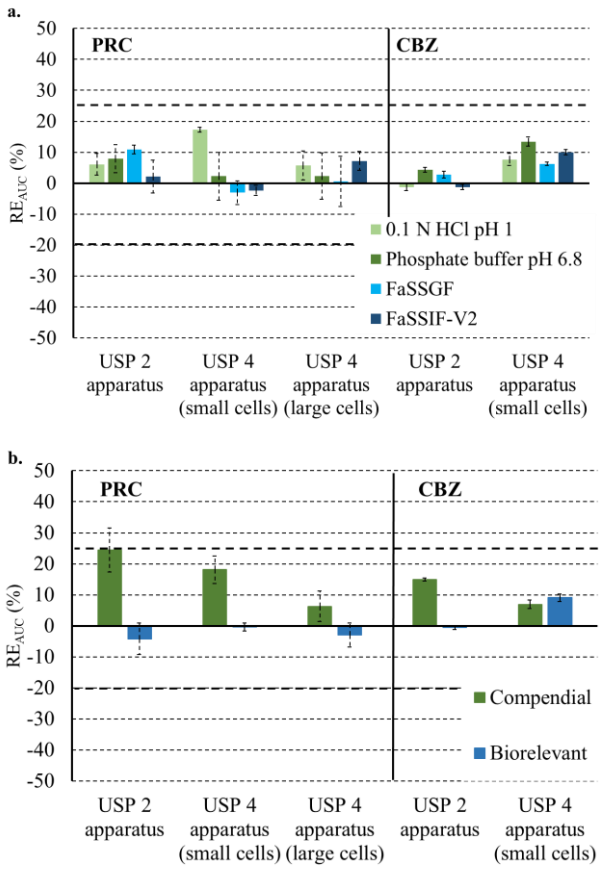


Figure 5.4: a. Relatives effects of excipients on the AUCs of the dissolution profiles between the control and HPMC variant tablets for the dissolution of PRC and CBZ in compendial (green colour) and biorelevant (blue colour) media in the studied apparatuses. Light and dark colours correspond to acidic and basic conditions, respectively (Mean ± SD, n = 3). b. Relative effects of excipients on the AUCs of the dissolution profiles between acidic and basic conditions for the dissolution of PRC and CBZ from the HPMC variant tablets in compendial (green colour) and biorelevant (blue colour) media. (Mean ± SD, n = 3)

Positive RES_{AUC} were observed in all experimental conditions (0.6% < REs < 17%) apart from the case of drug dissolution in biorelevant media in the USP 4 apparatus (small cells) (RES_{AUC} of -3% and -2.3% in FaSSGF and FaSSIF-V2, respectively). The positive RES_{AUC} indicated slightly more complete drug dissolution from the HPMC variant tablets compared to the control tablets due to the faster tablet disintegration (**Table 5.3**). The dissolution profiles of the HPMC variant tablets and the control tablets were similar (f_2 > 50) in all experimental conditions (**Table 5.4)**,

indicating that varying HPMC viscosity type is not expected to be critical for the dissolution of highly soluble compounds from immediate release formulations . A dissolution medium effect in PRC dissolution from the HPMC variant tablets was revealed, as drug dissolution was slightly more complete in basic compared to acidic conditions in compendial (RES_{AUC} of 24%, 18% and 6% in the USP 2, USP 4 (small cells) and USP 4 (large cells) apparatus, respectively) but not in biorelevant media (**Figure 5.4b**). This differences in PRC dissolution in basic compared to acidic compendial media is attributed to the presence of SSG and MgSt (as explained in 3.2.1.1.), therefore it is concluded that changes in the viscosity type of HPMC are not expected to affect the performance of other excipients in immediate release tablets.

Table 5.4: Similarity factors (f_2) of the dissolution profile comparisons for PRC and CBZ variant tablets in compendial and biorelevant media using the USP 2 and USP 4 (small and large cells) apparatuses. Bold values indicate significant differences between the test and the reference dissolution profiles ($f_2 < 50$).

		Compendial Media				Biorelevant Media			
		0.1 N HCl pH 1		Phosphate buffer pH 6.8		FaSSGF		FaSSIF-V2	
		PRC	CBZ	PRC	CBZ	PRC	CBZ	PRC	CBZ
USP 2 apparatus	HPMC Variant	62.9	83.8	67.2	70.9	59.5	76.3	85.4	86.2
	SSG Variant	69.7	63.6	64.4	67.3	65.0	65.4	83.6	76.7
	MgSt Variant	50.8	94.0	**47.1**	68.5	**43.0**	87.9	**41.2**	90.4
USP 4 apparatus (small cells)	HPMC Variant	55.8	58.8	72.0	56.4	83.5	67.6	71.6	62.1
	SSG Variant	77.7	64.2	62.6	56.8	70.3	59.1	72.3	61.2
	MgSt Variant	**34.0**	77.1	**46.2**	67.7	**45.0**	77.8	**42.1**	85.1
USP 4 apparatus (large cells)	HPMC Variant	65.6	-*	81.5	-	88.9	-	64.6	-
	SSG Variant	66.1	-	80.9	-	91.8	-	87.8	-
	MgSt Variant	58.2	-	61.6	-	63.0	-	56.0	-

*experiments not performed

5.3.2.2.2. Poorly soluble drug (CBZ)

Approximately, 80% (USP 2 apparatus) and complete (USP 4 apparatus) drug dissolution was reached in 4 hours from the HPMC variant tablets (**Figure 5.3**) reflecting the differences of the two dissolution experimental setups in achieving sink conditions [53]. The REs on the AUCs of the dissolution profiles for the HPMC variant tablets compared to the control tablets were minor in the USP 2 apparatus (-10% < RES_{AUC} < 10%) and slightly positive in the USP 4 apparatus (6% < RES_{AUC} < 13%) (**Figure 5.4a**). The dissolution profiles of the HPMC variant tablets and control tablets were similar (f_2 > 50) irrespective of medium or apparatus used (**Table 5.4)** revealing that varying HPMC viscosity type is not critical for the dissolution of poorly soluble drugs. Minor differences in drug dissolution in basic compared to acidic conditions (-0.5% < RES_{AUC} < 15%) were observed for the HPMC variant tablets (**Figure 5.4b**).

5.3.2.3. SSG Variant

5.3.2.3.1. Highly soluble drug (PRC)

Drug dissolution was complete from the SSG variant tablets in all experimental conditions (**Figure 5.1**). Differences in the time to reach 85% of drug dissolution between the SSG variant and the control tablets were observed only in phosphate buffer pH 6.8 and FaSSGF in the USP 2 apparatus (15 min vs 20 min for the SSG variant and control tablets, respectively) and in 0.1 N HCl pH 1 in the USP 4 apparatus (large cells) (45 min vs 30 min for the SSG variant and control tablets, respectively). The REs of excipients on the AUCs of the dissolution profiles between the SSG variant tablets and the control tablets were minor in all experimental conditions (-10% < RES_{AUC} < 10%) (**Figure 5.5a**) and dissolution profile comparisons (**Table 5.4**) revealed similarity between the dissolution profiles of the control and SSG variant tablets (f_2 > 50).

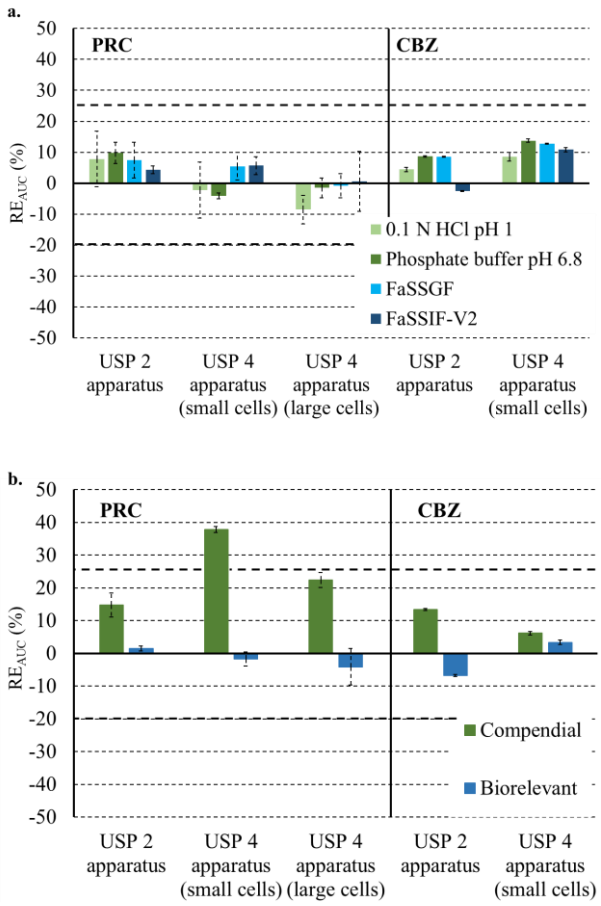


Figure 5.5: a. Relatives effects of excipients on the AUCs of the dissolution profiles between the control and SSG variant tablets for the dissolution of PRC and CBZ in compendial (green colour) and biorelevant (blue colour) media in the studied apparatuses. Light and dark colours correspond to acidic and basic conditions, respectively. (Mean ± SD, n = 3). b. Relative effects of excipients on the AUCs of the dissolution profiles between acidic and basic conditions for the dissolution of PRC and CBZ from the SSG variant tablets in compendial (green colour) and biorelevant (blue colour) media. (Mean ± SD, n = 3)

The positive REs on the AUCs of the dissolution profiles from the comparisons of dissolution performance in the tested media indicated more complete drug dissolution in basic compared to acidic conditions from the SSG variant tablets in compendial media (**Figure 5.5b**). In compendial media, the REs on the AUCs of the dissolution profiles of the SSG variant tablets between acidic and basic conditions (USP 2 apparatus: 15%, USP 4 apparatus (small cells): 38%, USP 4 apparatus (large cells:

22%) were more pronounced compared to the control tablets (USP 2 apparatus: 12%, USP 4 apparatus (small cells): 32%, USP 4 apparatus (large cells: 10%). These differences in drug dissolution between the SSG variant tablets and control tablets may be attributed to the fast and extensive swelling of low viscosity SSG in basic media [59].

5.3.2.3.2. Poorly soluble drug (CBZ)

The dissolution of CBZ from the SSG variant tablets was incomplete (70% - 80%) and complete in the USP 2 and USP 4 apparatus, respectively (**Figure 5.3**). The REs on the AUCs of the dissolution profiles of the SSG variant tablets were slightly positive in all experimental conditions ($4.5 < RES_{AUC} < 14\%$) apart from the case of drug dissolution in FaSSIF-V2 in the USP 2 apparatus ($RE_{AUC} = -2.5\%$) (**Figure 5.5a**). The dissolution profiles of the SSG variant tablets and the control tablets were similar in all experimental conditions ($f_2 > 50$) (**Table 5.4**) indicating that varying SSG viscosity type is not significant for the dissolution of poorly soluble drugs. Slightly more complete drug dissolution in basic compared to acidic conditions was observed ($3\% < RES_{AUC} < 13\%$) except from the case of drug dissolution in biorelevant media in the USP 2 apparatus ($RE_{AUC} = -6\%$) (**Figure 5.5b**).

5.3.2.4. MgSt Variant

5.3.2.4.1. Highly soluble drug (PRC)

Drug dissolution from the MgSt variant tablets was complete in all experimental conditions (**Figure 5.1**). The 85% of drug dissolution from the MgSt variant tablets was reached faster compared to the control tablets in compendial media and in FaSSGF in the USP 2 apparatus (15 min vs 20 min for the MgSt variant and control tablets, respectively). The time to reach 85% of drug dissolved was faster in 0.1 N HCl pH 1 (20 min vs 30 min for the MgSt variant and control tablets, respectively) and in phosphate buffer pH 6.8 and biorelevant media in the USP 4 apparatus (small cells) (15 min vs 20 min for the MgSt variant and control tablets, respectively). No differences in the time to reach 85% of drug dissolution were observed in FaSSIF-V2 (USP 2 apparatus) and in all experimental conditions (USP 4 apparatus (large cells)) between the MgSt variant and the control tablets. The REs of excipients on the AUCs of the dissolution profiles of the MgSt variant tablets compared to the control tablets

were positive (8% < RES_{AUC} < 41%), except from the case of drug dissolution in FaSSGF in the USP 4 apparatus (large cells) (RE_{AUC} = -0.7%) (**Figure 5.6a**). The positive RES_{AUC} indicate more complete drug dissolution as the low particle size MgSt produced softer tablets with faster disintegration (**Table 5.3**). Drug dissolution from the MgSt variant tablets was significantly faster compared to the control tablets in phosphate buffer pH 6.8 (f_2 = 47.1), FaSSGF (f_2 = 43.0) and FaSSIF-V2 (f_2 = 41.2) in the USP 2 apparatus and in all the studied media in the USP 4 apparatus (small cell) (34.0 < f_2 < 46.2) (**Table 5.4**) indicating the criticality of MgSt variability for the dissolution of highly soluble drugs. The significant changes in drug dissolution between the control and MgSt variant tablets reveal the effects of the applied hydrodynamics on the impact of excipient variability on drug dissolution. Significant differences in drug dissolution were observed in the USP 2 apparatus and the USP 4 apparatus (small cells) compared to the USP 4 apparatus (large cells), as the discriminatory power of the dissolution method increases with increased fluid velocities or Reynolds numbers [55, 60] (explained in section 3.2.1.1).

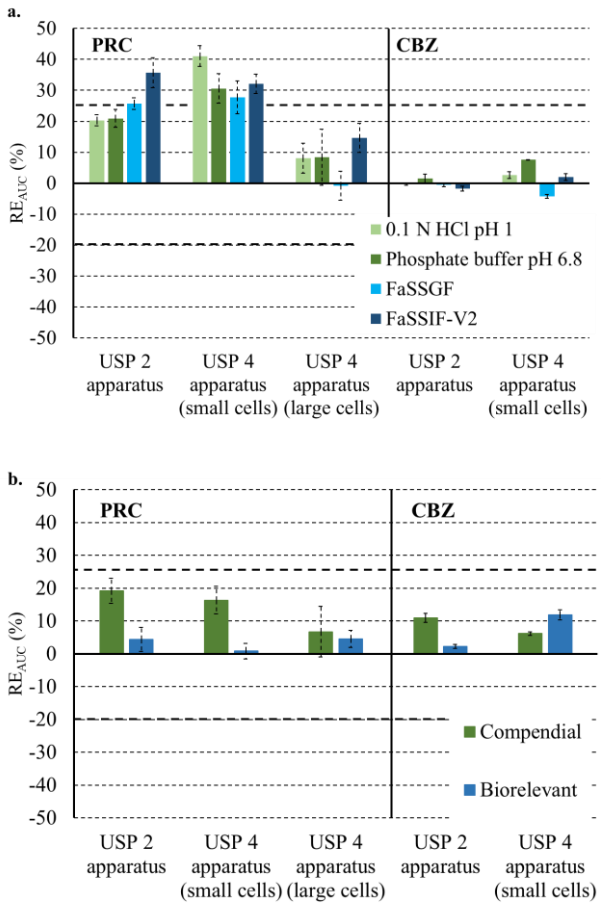


Figure 5.6: a. Relatives effects of excipients on the AUCs of the dissolution profiles between the control and MgSt variant tablets for the dissolution of PRC and CBZ in compendial (green colour) and biorelevant (blue colour) media in the studied apparatuses. Light and dark colours correspond to acidic and basic conditions, respectively (Mean ± SD, n = 3). b. Relative effects of excipients on the AUCs of the dissolution profiles between acidic and basic conditions for the dissolution of PRC and CBZ from the MgSt variant tablets in compendial (green colour) and biorelevant (blue colour) media. (Mean ± SD, n = 3)

In compendial media, more complete drug dissolution (6% < RES_{AUC} < 19%) from the MgSt variant tablets in basic compared to acidic conditions was observed revealing the pH-depended performance of MgSt (**Figure 5.6b**).

5.3.2.4.2. Poorly soluble drug (CBZ)

Approximately, 70% - 80% (USP 2 apparatus) and 90% (USP 4 apparatus) of CBZ dissolved from the MgSt variant tablets (**Figure 5.3**). The REs on the AUCs of the dissolution profiles of the MgSt variant tablets compared to the control tablets were minor in all experimental conditions (-10% < RES_{AUC} < 10%) (**Figure 5.6a**). Dissolution profile comparisons (**Table 5.4**) revealed that drug dissolution from the MgSt variant tablets was similar to the control tablets in all experimental conditions (f_2 > 50). Slightly more complete drug dissolution was observed in basic compared to acidic conditions (2% < RES_{AUC} < 12%) from the MgSt variant tablets (**Figure 5.6b**).

5.3.3. Real time surface dissolution UV imaging

The real-time surface dissolution UV visualization of the disintegration/dissolution phenomena for the PRC and CBZ tablets tested is presented in **Figure 5.7**.

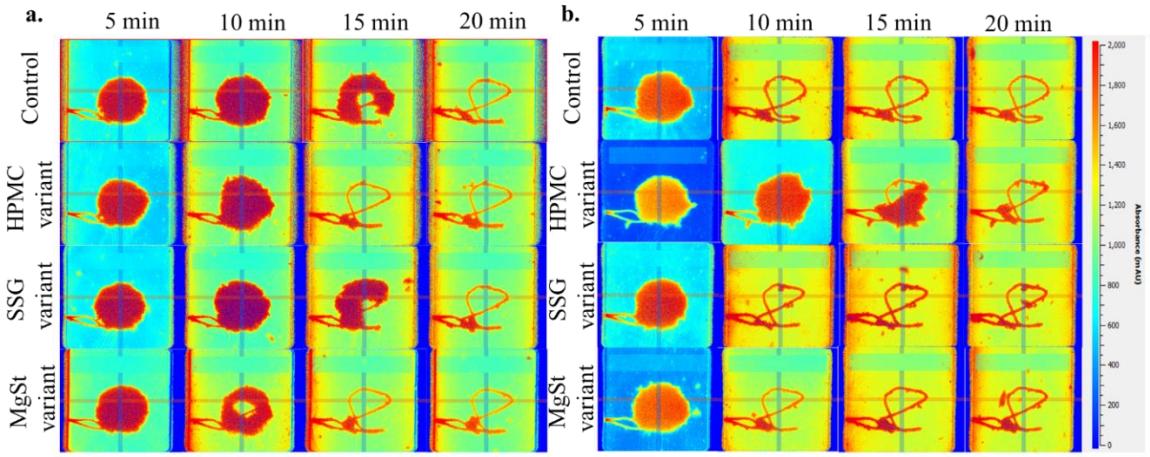


Figure 5.7: Real-time surface dissolution UV images for a. PRC and b. CBZ tablets in 0.1 N HCl pH 1.

The PRC and CBZ control tablets fully disintegrated at 16 min and 8 min, respectively. The dissolution profiles of the PRC and CBZ tablets are presented in **Figure 5.8**. Complete dissolution was not observed for any of the studied drugs. After 20 min, approximately 70% of PRC and 10% of CBZ dissolved from the control tablets, reflecting the differences in the dissolution rates of highly and poorly soluble drugs.

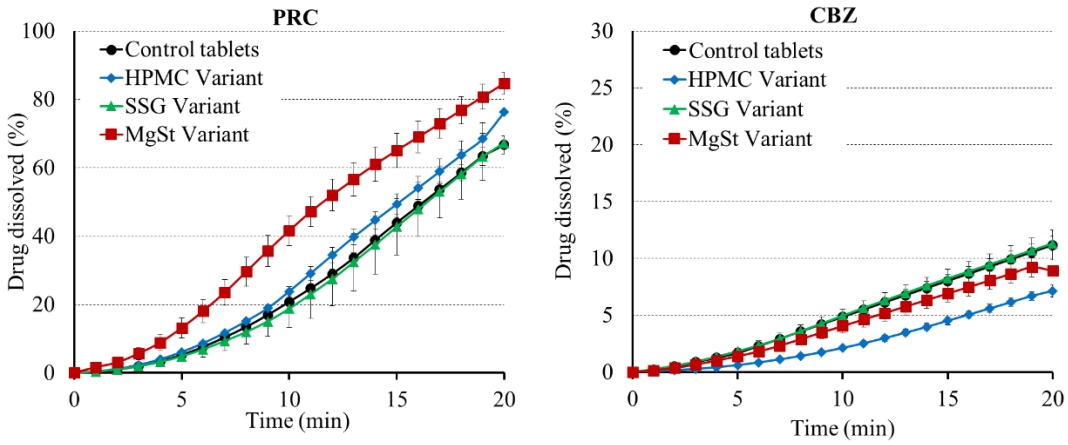


Figure 5.8: Dissolution profiles of PRC and CBZ from the i. Control tablets (black circles), ii. HPMC variant tablets (blue diamonds), iii. SSG variant tablets (green triangles) and iv. MgSt variant tablets (red squares) in 0.1 N HCl pH 1 using surface dissolution UV Imaging (SDi2, 6.16 mL/min, 37 °C, open mode). (Mean ± SD, n = 3)

In the case of PRC, tablet disintegration (13 min) (**Figure 5.7**) and drug dissolution (76% of drug dissolved at 20 min) were faster from the HPMC variant tablets compared to the control tablets (tablet disintegration at 16 min, 70% of drug dissolved at 20 min). These differences could be attributed to the lower tablet hardness of the HPMC variant compared to the control tablets (**Table 5.3**). For CBZ, slower disintegration (17 min) and drug dissolution (7% of drug dissolved at 20 min) was observed from the HPMC variant compared to the control tablets (tablet disintegration at 8 min, 10% of drug dissolved at 20 min). Changing the viscosity type of HPMC did not affected the hardness of CBZ tablets (as the impact of excipients on tablet hardness was pronounced for the highly soluble drug which inherently produced stronger tablets, **Table 5.3**). Therefore the slower tablet disintegration and drug dissolution from the HPMC variant compared to the control tablets could be attributed to the differences in the viscosity type of the used HPMC brands. The REs on the AUCs of the dissolution profiles revealed minor differences between the studied tablets for PRC (RE_{AUC} = -13%) and significant slower drug dissolution from the HPMC variant tablets (RE_{AUC} = -48%) for CBZ due to the slower disintegration (**Figure 5.7**). The disintegration time of the SSG variant tablets was similar to the control tablets for both

PRC (16 min) and CBZ (9 min). Differences in drug dissolution when varying SSG brand were not observed for any of the studied drugs (PRC: 70% of drug dissolved at 20 min, CBZ: 10% of drug dissolved at 20 min) and confirmed by the minor REs of excipients on the AUCs of the dissolution profiles (PRC: RE_{AUC} = -7%, CBZ: RE_{AUC} = 2%). Faster disintegration was observed for the MgSt variant tablets (11 min) compared to the control tablets (16 min) for PRC resulting in significantly faster drug dissolution (85% of drug dissolved at 20 min for the MgSt variant tablets compared to 70% of drug dissolved at 20 min for the control tablets) (RE_{AUC} = 65%), that could be attributed to the lower tablet hardness of the MgSt variant tablets (**Table 5.3**). Differences in tablet disintegration (9 min) and drug dissolution (9% of drug dissolved at 20 min) between the MgSt variant tablets and the control tablets were not observed in the case of CBZ, as the hardness of the CBZ tablets was not affected when decreasing the particle size of MgSt (**Table 5.3**). The RE of excipients on the AUCs of the dissolution profiles for CBZ was close to the lower limit of the reference range criterion (RE_{AUC} = -21%) indicating that slight differences in drug dissolution may be expected at early time points when varying MgSt. The real-time surface dissolution UV imaging confirmed that for immediate release formulations, excipients may alter drug dissolution due to their effects on tablet disintegration and/or tablet wetting. The impact of excipient variability on drug dissolution depends both on excipient and drug characteristics as significant differences were mainly observed for PRC when varying the MgSt brand and CBZ when varying the HPMC brand. The disintegration data from the real-time surface dissolution UV images are in good agreement with the data from the compendial disintegration test (**Table 5.3**). The results confirm that real-time surface dissolution UV imaging can give additional visual insights on tablet disintegration and drug dissolution in a biorelevant perspective.

5.3.4. Correlation of drug solubility and drug dissolution performance in presence of excipients

The REs of excipients on the AUCs of the dissolution profiles of the variant tablets as a function of the REs of excipients on drug apparent solubility in compendial and biorelevant media are presented in **Figure 5.9**.

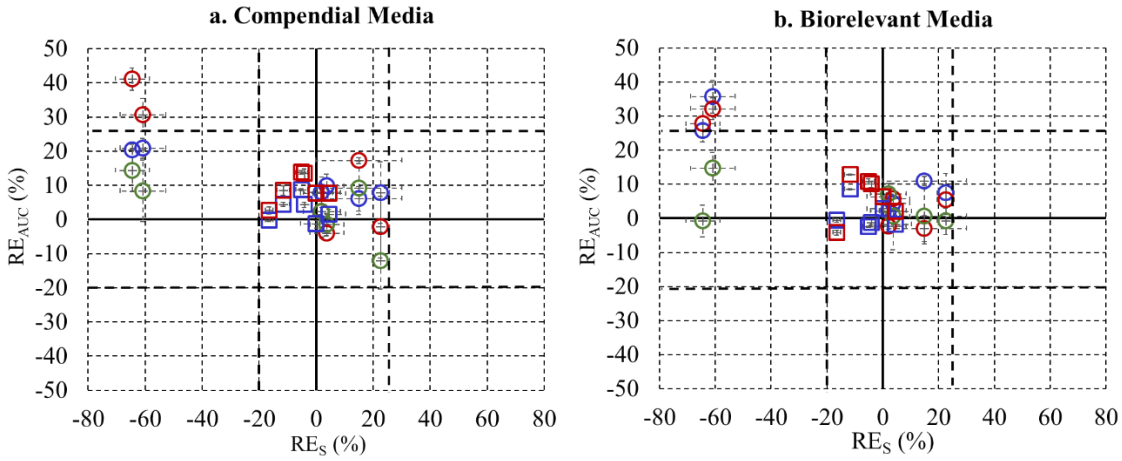


Figure 5.9: Relative effects of the studied excipients on the AUCs of the dissolution profiles (RE_{AUC}) as a function of relative effects of the studied excipients on drug solubility (RE_S) in a. compendial and b. biorelevant media. The drugs are portrayed as: i. PRC (circles) and ii. CBZ (squares). The dissolution profiles with the studied apparatuses are shown as: i. USP 2 apparatus (blue colour), ii. USP 4 apparatus – small cells (red colour) and iii. USP 4 apparatus - large cells (green colour). (Mean ± SD, n = 3)

In cases where significant changes in drug apparent solubility were not observed when varying excipient brands ($-20\% < REs_S < 25\%$), drug dissolution was not greatly affected by excipient variability, as indicated by the low REs of excipients on the AUCs of the dissolution profiles ($-20\% < REs_{AUC} < 25\%$). In cases where excipient variability significantly altered drug solubility, drug dissolution was affected by the excipient change and depended on the applied hydrodynamics. This was the case of PRC in presence of MgSt, where the low particle size brand (Ligamed MF-3-V) decreased drug solubility to a higher extent compared to the high particle size brands (Ligamed MF-2-V). This was attributed to i. the higher lubrication efficiency of the low particle size brand around drug particles or ii. drug shielding by the presence of a more lipophilic MgSt brand (Chapter 2). The faster drug dissolution relates to the low particle size of the MgSt variant brand (Ligamed MF-3-V) as due to its improved lubrication efficiency it produced softer tablets. As the hardness of the CBZ control tablets was lower compared to the PRC (**Table 5.3**), the impact of varying MgSt brand was not pronounced for the poorly soluble compound. Differences in the dissolution

profiles of PRC when varying MgSt brand were more pronounced in the USP 2 apparatus and USP 4 apparatus – small cell (20% < RES_{AUC} < 41%) compared to the USP 4 apparatus – large cells (RES_{AUC} < 20%) due to the differences in the applied hydrodynamics, as explained previously (section 2.3.4.1). For the highly soluble drug, in the cases where an average correlation between the impact of excipients on drug dissolution and drug solubility was observed (RE_{AUC} ≈ 20%, close to the upper limit of risk assessment criteria), dissolution profile comparisons can still prove differences in drug dissolution (**Table 5.4**). The aforementioned correlations indicate that drug solubility studies give an insight on the impact of excipient variability on drug dissolution, as for the majority of cases the effects of excipients on drug dissolution and drug solubility were well correlated, apart from the case of PRC dissolution in the USP 4 apparatus (large cells) when varying MgSt (no significant changes in drug dissolution attributed to the low fluid velocities of the system [60]).

5.3.5. Multivariate data analysis of *in vitro* dissolution data

The standardized beta coefficients of the variables in compendial and biorelevant media are presented in **Figure 5.10**. The two models showed a good predictive power and fit (compendial media: $Q^2 = 0.5$, $R^2 = 0.6$, biorelevant media: $Q^2 = 0.5$, $R^2 = 0.6$).

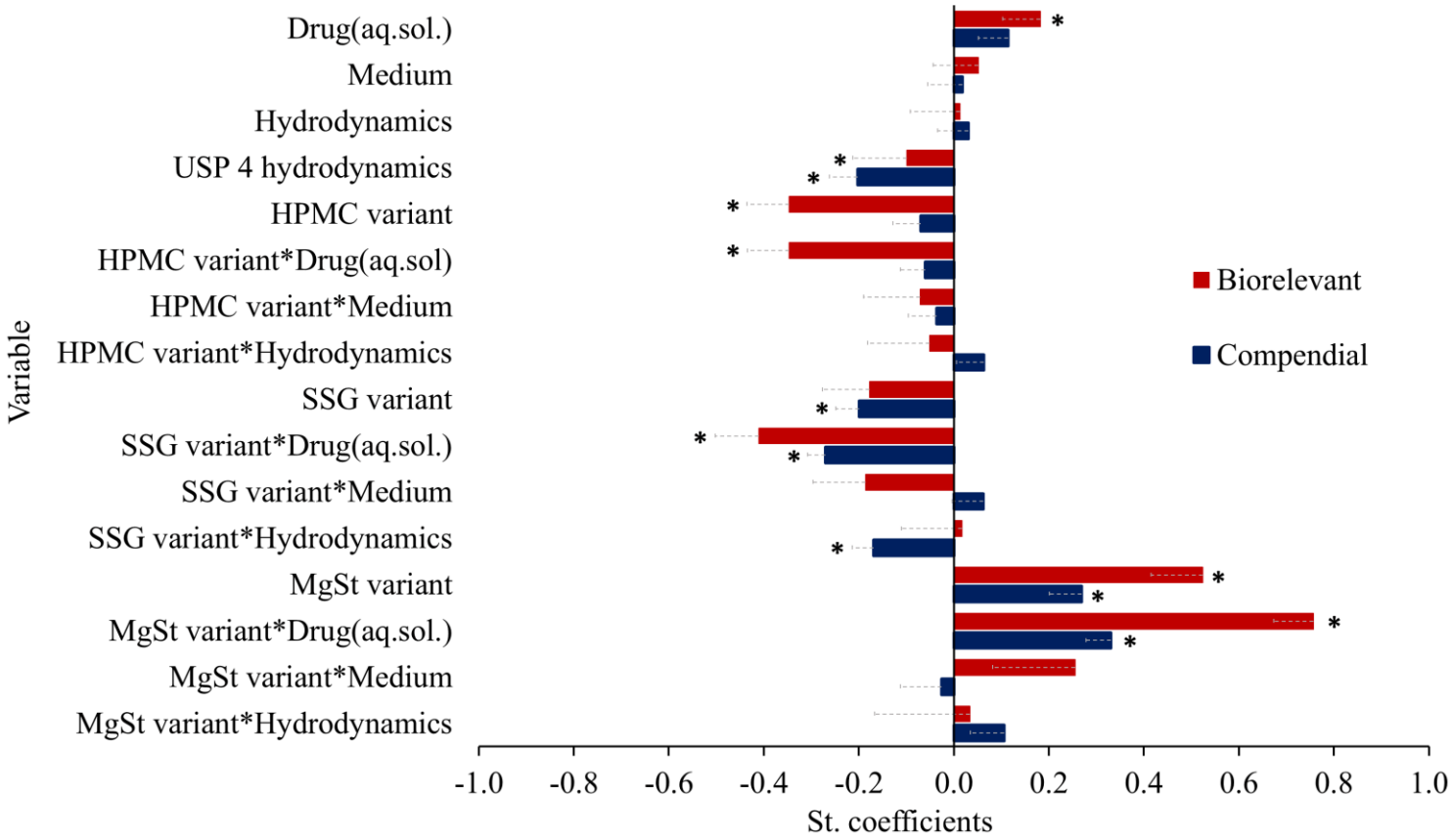


Figure 5.10: Standardized coefficients of the studied variables (and interaction terms) in compendial (blue colour) and biorelevant (red colour) media. * denotes coefficients of VIP > 1. * denotes coefficients of 0.8 < VIP < 1. (Mean, - SE)

The statistical analysis reveals that the impact of excipient variability on drug dissolution depends on the excipient variant. MgSt variant (compendial media, positive effect, VIP = 1.7, biorelevant media, positive effect, VIP = 1.6) was a significant variable in both models revealing that faster drug dissolution is anticipated from tablets containing MgSt of low particle size due to the production of softer tablets with faster tablet disintegration compared to tablets containing MgSt of high particle size. SSG variant (compendial media: negative effect, VIP = 1.3) and HPMC variant (biorelevant media: negative effect, VIP = 1.0) were significant variables in the indicated models. The negative effect of these variables reveals that varying SSG or HPMC viscosity type may result in slightly slower drug dissolution or that the improvement in drug dissolution will be lower when varying the aforementioned brands compared to MgSt. The impact of excipient variability on drug dissolution also related to drug aqueous solubility as revealed by the significance of the variable $Drug_{(aq.sol.)}$ (positive effect, VIP = 1.2) in the biorelevant model. This variable indicates that significantly faster drug dissolution when varying excipient types is anticipated for the highly soluble drug, as excipient variability may strongly affect tablet properties of hydrophilic components (**Table 5.3**). The significance of the variable $Drug_{(aq.sol.)}$ in biorelevant (and not in compendial) media indicates that changes in drug dissolution will be pronounced in media where tablets disintegrate fast, due to the presence of the solubilizing components which improve tablet wetting [8]. The effects of excipient on drug dissolution depends also on the hydrodynamics, as revealed by the significance of the USP 4 hydrodynamics (compendial media: negative effect, VIP 1.3, biorelevant media: negative effect, VIP = 1) in both models. This variable indicates that the improvement in drug dissolution by the studied excipients in the USP 4 apparatus will be less pronounced when the large cells are used, as differences in drug dissolution rates cannot be observed in very low fluid velocities [55].

The complex nature of excipient variability and its impact on drug dissolution was identified by the significance of certain interactions between the studied variables. MgSt variant* $Drug_{(aq.sol.)}$ was a significant variable (compendial media: positive effect, VIP = 2.1, biorelevant media: positive effect, VIP = 2.4) in both models and reveals that the enhancement in drug dissolution by low particle size MgSt brands will be pronounced for highly soluble drugs (due to the differences in tablet hardness). SSG variant* $Drug_{(aq.sol.)}$ (compendial media: negative effect, VIP = 1.7, biorelevant media:

negative effect, VIP = 1.3) and HPMC variant* $Drug_{(aq.sol.)}$ (biorelevant media: negative effect, VIP = 1.0) were significant interactions in the models. These interactions reveal that the enhancement in drug dissolution when varying SSG or HPMC viscosity will be less pronounced for the highly soluble drug, as, generally, presence of hydrophilic excipients may improve the dissolution of poorly soluble drugs. Finally, SSG variant*hydrodynamics (negative effect, VIP = 1.0) was a significant variable in the compendial model revealing that varying SSG variant may result in slightly slower drug dissolution or that the improvement in drug dissolution will be lower with decreasing flow velocities [55, 60].

5.4. Conclusions

Dissolution testing plays a key role in QbD approaches assessing the quality and biorelevant or clinical performance of final dosage forms. Excipient presence and variability may present challenges for oral drug absorption, therefore understanding the biopharmaceutical implications of excipients on product performance with the use of dissolution tests is beneficial. In this work, the impact of excipient variability of binders (HPMC – viscosity type), superdisintegrants (SSG – viscosity type) and lubricants (MgSt – PSD type) on the dissolution of a highly and a poorly soluble drug from immediate release formulations was assessed in a biopharmaceutical perspective. Varying MgSt brand was considered of high criticality for oral drug performance as faster dissolution was observed for the highly soluble drug due to the production of softer tablets when decreasing the particle size of MgSt. Dissolution profile comparisons revealed that MgSt variant tablets would not meet the quality control acceptance criteria and could present regulatory implications. The impact of hydrodynamics on the effects of MgSt variability on drug dissolution was revealed, as increasing flow velocities (for the highly soluble drug) resulted in dissolution methods with better discriminatory power. Varying HPMC or SSG grade was of low criticality for product performance as similarity was found between the dissolution profiles of the control and variant tablets irrespective of the model compound. The pH and presence of solubilizing components affected the impact of excipients (especially SSG and MgSt) on drug dissolution. Real-time surface dissolution UV imaging revealed that varying excipient types/brands can affect tablet disintegration and/or wetting. *In vitro* dissolution data were in good agreement with previous solubility studies in presence of excipients showing that changes in drug solubility by excipient variability

may indicate significant changes in drug dissolution. Use of PLS revealed the significant role of excipient type and material attributes, drug aqueous solubility, medium characteristics and hydrodynamic conditions on the excipient effects on drug dissolution. The study highlights the effects of excipient variability on product performance and the importance of biopharmaceutical considerations for excipient selection.

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Chapter 5 Commentary

Dissolution testing can be used to assess the criticality of excipient variability on product performance in a Quality be Design (QbD) perspective. In this chapter, the impact of excipient variability of binders (viscosity type of hypromellose (HPMC)), superdisintegrants (viscosity type of sodium starch glycolate (SSG)) and lubricants (particle size distribution of magnesium stearate (MgSt)) on the dissolution of a highly and a poorly soluble drug was investigated in a biopharmaceutical perspective. Dissolution tests were performed in compendial and biorelevant media using compendial apparatuses (USP 2 and USP 4 apparatus) and surface dissolution UV imaging. The impact of excipients on drug dissolution depended on the excipient type used. Significant changes in drug dissolution when varying HPMC or SSG viscosity type were not observed for the studied drugs. The high criticality of MgSt was demonstrated (as also revealed in Chapter 2). Decreasing the particle size of MgSt resulted in faster drug dissolution for the highly soluble drug as a result of the lower tablet hardness caused by the lipophilic nature of the excipient. These results demonstrate that the impact of excipients on drug dissolution strongly relate to the excipient type used and the drug under investigation. The interplay of excipient critical material properties and manufacturing processes and their impact on drug dissolution was revealed. Differences in drug dissolution, when varying MgSt, were more pronounced in apparatuses of high flow velocities indicating that the effects of different excipient brands can depend on the gastrointestinal hydrodynamics. Additional insights on the impact of excipients on drug dissolution were obtained with the use of surface dissolution UV imaging which allowed the real-time visualization of tablet disintegration and wetting phenomena. The importance of designing biorelevant methods to study excipient criticality was demonstrated with the use of multivariate data analysis.

Chapter 6 Preface

Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) are two commonly used swelling superdisintegrants that promote fast tablet disintegration in immediate release formulations. Their superior performance, compared to natural polymers, is attributed to the crosslinking and carboxymethylation of the polymeric chains. Differences in the swelling capacity between SSG and CCS, despite their similar structure, have been attributed to their varying physicochemical properties. Excipient interchangeability, therefore, is questionable as changes in tablet disintegration and drug dissolution can be anticipated when varying excipients with the same intended functionality. The critical material properties and the biopharmaceutical implications of superdisintegrants are not fully understood. The previous chapters focused on understanding the effects of superdisintegrant variability on drug apparent solubility and drug dissolution. As superdisintegrants act in seconds, use of surface dissolution UV imaging (novel approach which allows the spatial and temporal visualization of disintegration and/or dissolution phenomena) could give further mechanistic insights on superdisintegrant functionality. The aims of this chapter are to assess the swelling performance of SSG and CCS with different material properties and identify their impact on the dissolution of a highly and a poorly soluble drug using surface dissoluton UV imaging. Acidic and basic compendial media will be used to identify the role of the pH of the medium on the swelling behaviour of superdisintegrants and how this could influence drug dissolution.

Chapter 6. Surface dissolution UV Imaging for characterization of superdisintegrants and their impact on drug dissolution

Abstract

Superdisintegrants are a key class of excipients used in immediate release formulations to promote fast tablet disintegration, therefore understanding the impact of superdisintegrant variability on product performance is important. The current study examined the impact of superdisintegrant critical material attributes (viscosity for sodium starch glycolate (SSG), particle size distribution (PSD) for croscarmellose sodium (CCS)) on their performance (swelling) and on drug dissolution using surface dissolution UV imaging. Acidic and basic pharmacopoeia (compendial) media were used to assess the role of varying pH on superdisintegrant performance and its effect on drug dissolution. A highly soluble (paracetamol) and a poorly soluble (carbamazepine) drug were used as model compounds and drug compacts and drug-excipient compacts were prepared for the dissolution experiments. The presence of a swelled SSG or CCS layer on the compact surface, due to the fast excipient hydration capacity, upon contact with dissolution medium was visualized. The swelling behaviour of superdisintegrants depended on excipient critical material attributes and the pH of the medium. Drug dissolution was faster in presence compared to superdisintegrant absence due to improved compact wetting or compact disintegration. The improvement in drug dissolution was less pronounced with increasing SSG viscosity or CCS particle size. Drug dissolution was slightly more complete in basic compared to acidic conditions in presence of the studied superdisintegrants for the highly soluble drug attributed to the increased excipient hydration capacity and the fast drug release through the swelled excipient structure. The opposite was observed for the poorly soluble drug as potentially the improvement in drug dissolution was compromised by drug release from the highly swelled structure. The use of multivariate data analysis revealed the influential role of excipient and drug properties on the impact of excipient variability on drug dissolution.

Keywords: excipient viscosity, excipient particle size, sodium starch glycolate, croscarmellose sodium, excipient swelling, real – time surface dissolution UV imaging

6.1. Introduction

Presence of superdisintegrants in oral solid dosage forms is essential for fast tablet disintegration and improved drug dissolution. Sodium starch glycolate (SSG)) and Croscarmellose sodium (CCS) (semisynthetic polymers of starch and cellulose, respectively) are commonly used as superdisintegrants in tablet manufacturing. The main mechanism by which superdisintegrants promote tablet disintegration is swelling [1]. Swelling refers to the volume expansion of the superdisintegrant particles upon contact with water [1]. The swelling mechanism of SSG and CCS has been confirmed with the use of real-time magnetic resonance imaging [2].

SSG and CCS are sodium salts and are present as a neutral form in acidic and ionized form in basic conditions. They derive from natural polymers after two main modification steps (carboxymethylation and crosslinking) of the natural polymer chains to improve excipient functionality [1]. Firstly, carboxymethylation (also known as degree of substitution) of the natural polymer backbone increases polymer hydrophilicity and allows water access into the excipient [3]. Secondly, as natural polymers are partially soluble and their dissolution may increase the viscosity of the medium, crosslinking of the polymeric chains serves in decreasing the soluble content of the polymer. SSG is crosslinked through phosphate groups [4] while CCS through ester groups [5] (**Figure 6.1**). The superior performance of SSG and CCS as tablet disintegrants, compared to native polymers, is attributed to these two modification steps.

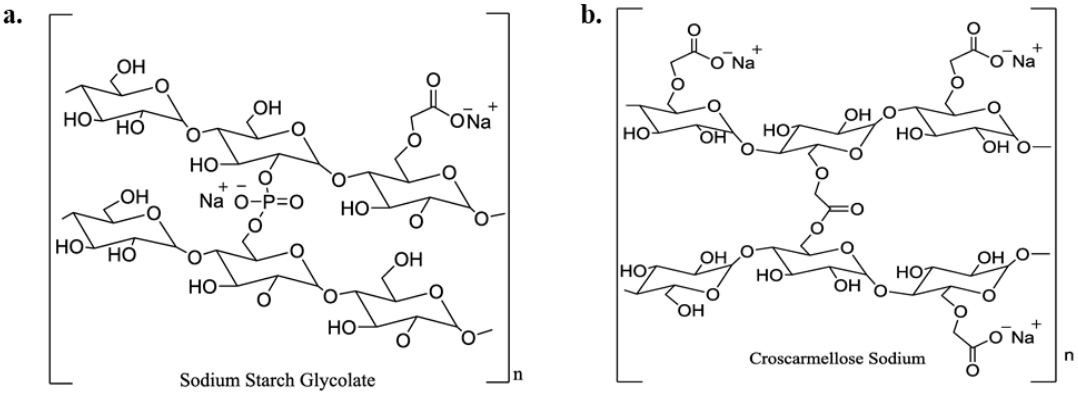

Figure 6.1: Chemical structure of a. Sodium Starch Glycolate and b. Croscarmellose Sodium (ChemDraw Professional 15)

The extensive and fast swelling of SSG and CCS is demonstrated by the increase in their volume median diameter (average volumetric size) upon contact with water (123 μm upon contact with water vs 35 μm of the dry excipient powder for SSG, 92 μm upon contact with water vs 45 μm of the dry excipient powder for CCS) and the amount of liquid water uptake (16 g/g and 10 g/g in 120 sec for SSG and CCS, respectively) [6]. The differences in the swelling capacity of SSG and CCS, despite their similar structure, have been attributed to the difference in their dimensional expansion (3-dimensional swelling for SSG, 2-dimensional swelling for CCS) [6, 7] and their different crosslinking (the phosphate group of SSG, compared to the ester group of CCS, allows for more spacing between the polymeric chains) [7]. Molecular properties (degree of substitution, degree of crosslinking), particle properties (particle size distribution (PSD)) and level have been identified as potential critical material attributes for SSG and CCS affecting product performance [8]. Increasing the degree of substitution of SSG and CCS results in faster water uptake and excipient swelling, however optimum values need to be defined as high degrees of carboxymethylation may result in an increase in the viscosity of the medium [8]. Extensive swelling and faster disintegration have been reported when increasing the degree of crosslinking, particle size or level in formulations for SSG and CCS [8].

The biopharmaceutical implications of superdisintegrant presence or variability on product performance are not well known. Gastrointestinal factors may impact the performance of superdisintegrants with pH being the most influential due to the ionization pattern of SSG and CCS. The hydration capacity of the acid excipient form in acidic media is lower compared to the ionized excipient form in basic media leading to reduced swelling in acidic conditions [6]. The % increase in the volume media diameter in water and 0.1 N HCl pH 1 was 251% and 43%, respectively for SSG and 104% and 51%, respectively for CCS [6]. The impact of superdisintegrants on product performance relates also to drug properties. Interaction of cationic drugs with the carboxylic group of CCS can affect routine drug analysis. Loss of the active pharmaceutical ingredient (API) from a tablet formulation containing CCS during sample treatment can be expected, as low % recovery of drugs (metformin [9], escitalopram [10]) from solutions in presence of CCS have been reported due to charge drug-excipient interactions. Delay in the dissolution of cationic drugs from immediate

release tablets containing SSG and CCS has also been attributed to electrostatic drug-excipient interactions [11].

Current approaches for assessing superdisintegrant performance and variability include the determination of: disintegration time of formulations, water uptake of powders/tablets, swelling volume of superdisintegrants, exerted force (force inside tablets that has to surpass the cohesive tablet forces) during tablet disintegration, dissolution rate of drugs, size of generated particles after tablet disintegration [1]. Real – time surface dissolution UV imaging is currently used in the pharmaceutical field providing additional information on disintegration/dissolution phenomena. This technique utilizes a compact flow-cell integrated with a UV-Vis camera and a pump for the infusion of the dissolution medium under laminar flow [12]. The measured transmittance of light through the cell allows the characterization of the dissolving substance spatially and temporally and is useful for the identification of drug intrinsic dissolution rates, surface swelling/disintegration/dissolution phenomena, concentration gradients and microenvironmental pH changes [13]. Insights in the dissolution behaviour of APIs [12], excipients [14] and their interplay [15, 16] have been provided with the use of real-time surface dissolution imaging.

The aims of this study were to assess the swelling performance of superdisintegrants with different critical material attributes and the impact and criticality of superdisintegrant variability on drug dissolution. Excipient characterization and drug dissolution studies in absence and presence of excipients were performed with the use of real-time surface dissolution UV imaging. The impact of excipient variability on excipient swelling and drug dissolution was studied by selecting three brands of SSG of different viscosity type and two brands of CCS of different PSD. A highly and a poorly soluble drug were used to assess the interplay of excipient variability and drug characteristics on drug dissolution. Studies were performed in acidic and basic compendial media to assess the role of pH on superdisintegrant swelling and drug dissolution.

6.2. Materials and Methods

6.2.1. Materials

APIs: Paracetamol was obtained from Fischer Scientific (UK). Carbamazepine was purchased from Fagron (UK). Excipients: Glycolys LV (low viscosity) and

Glycolys (high viscosity) (Roquette, France), AcDiSol (low particle size) (FMC, USA), Explotab CLV (low viscosity) (JRS Pharma, USA), Primellose (high particle size) (DFE Pharma, Germany) were obtained from the specified sources. Chemicals: Hydrochloric acid 36.5–38%, HPLC grade methanol were obtained from Sigma-Aldrich (UK). Sodium chloride, sodium hydroxide, potassium phosphate monobasic were obtained from Fisher Scientific (UK). Water was ultra-pure (Milli-Q) laboratory grade. Filters: Polytetrafluoroethylene (PTFE) 13 mm filter 0.45 μm pore size were purchased from Fisher Scientific (UK).

6.2.2. Instrumentation

Sartorius BP 210 D balance (Sartorius UK Ltd, UK), Mettler Toledo SevenCompact S210 pH meter (Mettler Toledo, Switzerland), Vortex-Genie 2 vortex mixer (Scientific Industries Inc, USA), Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A), autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector (G1329A) and a Chemstation software (Agilent Technologies, USA), Actipix SDi300 dissolution imaging system (Paraytec Ltd, UK) with an Actipix flow-through dissolution cartridge CADISS-2, Quickset Minor® torque screwdriver (Torqueleader, UK).

6.2.3. Methods

6.2.3.1. Media used for *in vitro* dissolution studied

Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to the method described in the United States Pharmacopeia [17].

6.2.3.2. Preparation of compacts

For the excipient characterization, 20 mg of each excipient were poured into the sample cup (stainless steel cylinder, inner diameter: 2 mm, height: 2.4 mm) and compacted using a manual press at a constant torque of 75 cNm for 5 min [14]. For the dissolution studies, compacts of pure APIs (paracetamol (PRC), carbamazepine (CBZ)) and compacts of superdisintegrants with the APIs were prepared. 10 mg of API (PRC, CBZ) were poured into the sample cup and compacts of pure API (drug compacts) were prepared using a manual press at a constant torque of 75 cNm for 5 min [14]. 10 mg of API and 2% w/w of each excipient (based on typical excipient amounts used in immediate release formulations [4, 5] were prepared by vortexing (3 min) and poured into the sample cup. Compacts of superdisintegrants with APIs (drug-

excipient compacts) were prepared using a manual press at a constant torque of 75 cNm for 5 min [14].

6.2.3.3. *In vitro* real-time surface dissolution UV imaging

Real-time surface dissolution UV Imaging was performed using an Actipix SDi300 surface dissolution imaging system with an Actipix flow-through-type dissolution cartridge. The flow cell consisted of an Actipix cartridge fitted with a quartz cell (7 mm height, 4 mm width, 62 mm length) and a polyetheretherketone (PEEK) sample holder. The light source was a pulsed xenon lamp and a band-pass filter (detection wavelength ± 10 nm) was used for the selection of the wavelength of interest. Dissolution medium was infused into the cell through a syringe pump. A temperature control unit was used to maintain constant temperature. The detection area of the UV imager was 9 mm^2 × 7 mm^2 (1280 pixel × 1024 pixel) with a pixel size of 7 μm × 7 μm. Detailed representation of the instrument has been previously presented [12, 18].

For the excipient characterization, experiments were performed at 254 nm using stagnant conditions for 5 min at 37 °C in 0.1 N HCl pH 1 and phosphate buffer pH 6.8. *In vitro* drug dissolution experiments from drug compacts and drug-excipient compacts were performed at 280 nm using 1 mL/min flow rate for 20 min at 37 °C in 0.1 N HCl pH 1 and phosphate buffer pH 6.8. For both the excipient characterization experiments and *in vitro* drug dissolution studies, dark (10 s duration with the lamp turned off) and reference (10 s duration with the lamp turned on) images were recorded with the flow cell filled with dissolution medium in absence of compact. Data collection was initiated and after 60 s data recording was pause and the compacts were introduced into the cell. The system was flushed with dissolution media to avoid presence of air bubbles in the flow cell and data collection was resumed. Pixel intensities within a designated quantification region were converted into absorbance values using the Actipix D100 software version 1.8.50805 (Paraytec Ltd, UK). In the *in vitro* drug dissolution experiments, the presence of the swelling excipients (SSG and CCS brands) in the quantification regions of the UV image resulted in increased scattering or physical blockage of light [18]. In these cases, the eluting sample was collected at 1 min intervals and the effluent samples were filtered through PTFE 0.45 μm pore size filters and analysed by HPLC. Filter adsorption studies were prior

performed in triplicate for each drug and confirmed that there were no adsorption issues for the studied drugs on the filters used. All experiments were performed in triplicate.

6.2.3.4. Chromatographic conditions

Dissolution samples (effluent collection) were analysed by HPLC. Analytical HPLC procedures were modifications of already published methods for PRC [19] and CBZ [20]. A reversed-phase Spherisorb (Waters) C18 column (250 × 4.6 mm, 5 μm) was used for both drugs. For PRC, the mobile phase consisted of methanol and water 20:80 (v/v) and the temperature was kept constant at 20 °C. The injection volume was 20 μL and the detection wavelength was at 257 nm. For CBZ, the mobile phase was composed of methanol and water 60:40 (v/v) and the temperature was kept at 25 °C. The injection volume was 100 μL and the detection wavelength was at 285 nm. The flow rate was set at 1 mL/min for both drugs (isocratic flow). The elution times were 6 min and 4 min for PRC and CBZ, respectively. Drug quantification was made based on calibration curves. Standards were prepared from concentrated stock solution of drug dissolved in MeOH (PRC: 2 mg/mL, CBZ: 1 mg/mL). The range of the calibration curves were 10 – 300 μg/mL and 0.5 -50 μg/mL for PRC and CBZ, respectively.

6.2.3.5. Treatment of *in vitro* dissolution data

For the characterization of the swelling superdisintegrant behaviour, quantitative data of excipient concentration gradients cannot be obtained due to i. the insolubility of the studied polymers and ii. the fact that the high absorbance values recorded may be attributed to absorbance or scattering of light by the swelled polymer or physical blockage of light by undissolved polymer particles [14]. Only qualitative information of the rate and extent of swelling can be obtained by the absorbance gradients as a function of distance from the center of the sample cup. Absorbance values (Abs) were automatically calculated from pixel intensities using the Actipix D100 software version 1.8.50805 (Paraytec Ltd, UK). The classification gradient maps depicting the swelling behaviour (absorbance values as a function of distance from the center of the sample cup) of the studied SSG and CCS brands in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 were generated using SigmaPlot 13.0 (Systat Software Inc, USA). The cumulative % of drug dissolved was calculated based on the measured drug

concentration in the samples (based on the HPLC analytical data) and the amount of drug in the compact. The dissolution profiles of the cumulative % of drug dissolved as a function time were constructed. Drug dissolution rates (μg/min) at each 1 min interval over the duration of the experiments were calculated based on the measured drug concentration in the samples (based on the HPLC analytical data) and the known flow rate of the dissolution experiments. Graphs depicting drug dissolution rates as a function of time (at 1 min intervals) were constructed and the standard deviation (SD) of the dissolution rates was presented in the midterm point of the sampling intervals.

The area under the curve (AUC) of the dissolution profiles up to last experimental time (20 min), calculated using the method of trapezoids, was used for the characterization of drug dissolution. The Relative Effect (RE) of each superdisintegrant on drug dissolution was calculated based on equation 6.1:

$$RE = \frac{(AUC_T - AUC_C)}{AUC_C} \, x \, 100 \qquad \text{equation 6.1}$$

where AUC_c and AUC_T are the areas under the curve of the dissolution profiles of the control and test compact, respectively. Two sets of comparisons were performed. In the first set (set 1), the differences in drug dissolution between drug compacts and drug-excipient compacts in each medium were examined taking the AUCs of the dissolution profiles of the drug compact and the drug-excipient compact as control and test dissolution profiles, respectively. In the second set (set 2), differences in drug dissolution within acidic and basic conditions in each drug-excipient compact were investigated taking the AUCs of the dissolution profiles in acidic and basic conditions as the control and test dissolution profiles, respectively. The risk assessment of the impact of excipients on drug dissolution was evaluated by setting reference range criteria of -20% - 25% [21] on the REs of excipients on the AUCs of the dissolution profiles (this range was selected as a similar range is set in order to assess differences in drug exposure after oral administration; i.e. in bioequivalence studies). REs of excipients on the AUCs of the dissolution profiles outside these values (REs < -20% or REs > 25%) were considered critical for oral drug performance.

6.2.3.6. Multivariate data analysis of *in vitro* dissolution data

Excipient REs on drug dissolution were correlated to excipient critical material attributes (viscosity for SSG, PSD for CCS), drug aqueous solubility ($Drug_{aq.sol.}$) and

medium (acidic, basic) characteristics by multiple linear regression (MLR) using the XLSTAT software (Microsoft, USA). Two models for the REs of excipients on the AUCs of the dissolution profiles in presence of SSG (Model 1) and CCS (Model 2) were constructed. The evaluated variables for both models were all categorical and included: i. drug aqueous solubility ($Drug_{aq.sol.}$) (0: poorly soluble, 1: highly soluble), ii. medium (0: acidic, 1: basic), iii. excipient brand (0: low excipient property, 1: high excipient property). Excipient REs on the AUCs of the dissolution profiles (set 1, section 6.2.3.5) were used as the response. The selected interaction terms included each excipient brand combined with each drug aqueous solubility and medium characteristics (acidic, basic). The generated MLR models were assessed in terms of goodness of fit (R^2) and variance inflation factor (VIF). High R^2 values and VIF values < 5 were indications of successful models with absence of multicollinearity among the independent variables [22]. Standardized coefficients were used to show the direction (positive or negative) and extent of each variable on the response. The significance of the variables was assessed by the p values ($p < 0.05$ were considered the most significant in the model [22]). A 95% confidence interval was used.

6.3. Results and Discussion

6.3.1. Characterization of the swelling behaviour of superdisintegrants using real-time surface dissolution UV Imaging

The studied excipient types and brands have been previously characterized in terms of viscosity for SSG and PSD for CCS (Chapter 4). The viscosity after 60 min of the aqueous dispersions of Glycolys LV (10.8 cP) and Explotab CLV (12.7 cP) was lower compared to Glycolys (20.9 cP), due to their higher degree of crosslinking and lower soluble material content [23]. Differences in the PSD of the CCS brands were identified, as AcDiSol comprised of smaller particles (d10: 12.8 μm, d50: 31.9 μm, d90: 74.2 μm) compared to Primellose (d10: 21.8 μm, d50: 52.2 μm d90: 109.8 μm).

The swelling behaviour of the studied superdisintegrants as a function of time and distance from the centre of the sample cup in 0.1 N HCl pH 1 is presented in **Figure 6.2**. Intense signals at the compact location are indications of dense swollen polymeric structures [15], as the high absorbance recorded are attributed to light scattering by the swelled superdisintegrants or physical blockage of light by undissolved excipient particles (as explained in section 6.2.3.5.). The fast excipient swelling was

demonstrated as all the studied superdisintegrants swelled at a distance of 1.2 mm from the centre of the sample cup at approximately 20 – 40 s irrespective of excipient type or brand. For SSG, Glycolys exhibited lower absorbance values (Abs ≈ 1.0 – 1.2 AU) compared to Glycolys LV and Explotab CLV (Abs ≈ 1.2 – 1.6 AU) probably due to the higher soluble content of high viscosity brands [23]. For CCS, the higher absorbance values of Primellose (Abs ≈ 1.4 – 1.6 AU) compared to AcDiSol (Abs ≈ 1.0 – 1.2 AU) can be attributed to the pronounced physical blockage of light by larger particles [24].

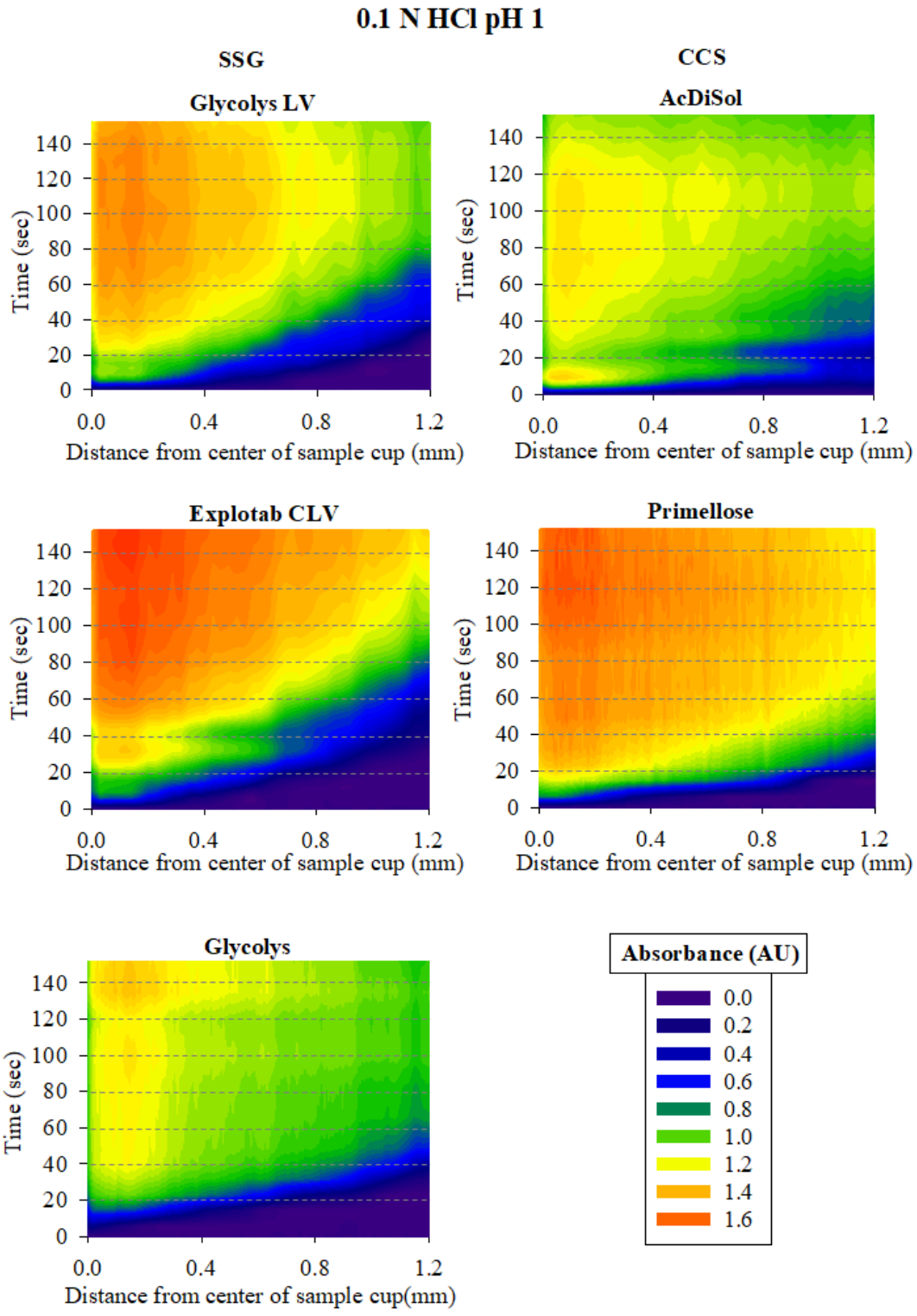

Figure 6.2: Absorbance values (Abs) of the studied superdisintegrant types and brands as a function of distance from the center of the sample cup (mm) in 0.1 N HCl pH 1 (SDi1, 0 mL/min, 37 °C, 254 nm) presented up to 2.5 min.

The swelling behaviour of the studied superdisintegrants as a function of time and distance from the centre of the sample cup in phosphate buffer pH 6.8 is presented in **Figure 6.3**. Slightly faster excipient swelling in phosphate buffer pH 6.8 (< 20 s) was observed compared to 0.1 N HCl pH 1 (20 – 40 s) explained by the higher liquid uptake (0.1 N HCl pH 1: approximately 5 g/g liquid uptake by SSG and CCS after 2 min , water: 18 g/g and 10 g/g liquid uptake by SSG and CCS, respectively after 2 min [6]) and excipient swelling of the ionized excipient form in basic media [6]. The absorbance values of the studied brands were lower in phosphate buffer pH 6.8 (SSG brands: 0.6 – 1.2 AU, CCS brands: 1.0 – 1.4 AU) compared to 0.1 N HCl pH 1 (SSG brands: 1.0 – 1.6 AU, CCS brands: 1.0 – 1.6 AU). We hypothesize that the lower absorbance values in the basic compared to the acidic medium relate to the higher excipient swelling, as the higher spacing of the swelled polymeric chains [7] could decrease the scattering or physical blockage of light. Differences in the absorbance values are not observed within the studied SSG brands (Abs ≈ 0.6 – 1.0 AU). For CCS, lower absorbance values were observed for AcDiSol (Abs ≈ 1.0 – 1.2 AU) attributed to its lower particle size compared to Primellose (Abs ≈ 1.2 – 1.4 AU) [24]. The lower absorbance values of the SSG compared to the CCS brands in phosphate buffer pH 6.8 can indicate a more extensive swelling by SSG, due to the differences in the dimensional expansion (3 dimensional swelling (semispherical particles) for SSG and 2 dimensional swelling (fibrous particles) for CCS upon contact with simulated intestinal fluid have been reported [7]) and type of crosslinking (phosphate groups for SSG, ester group for CCS) between the two excipient types [7]. The observed differences in excipient performance in the studied media indicate that differences in tablet disintegration between the stomach and the small intestine are anticipated (due to the differences in the pH of these two compartments) and could potentially implicate product performance and drug bioavailability.

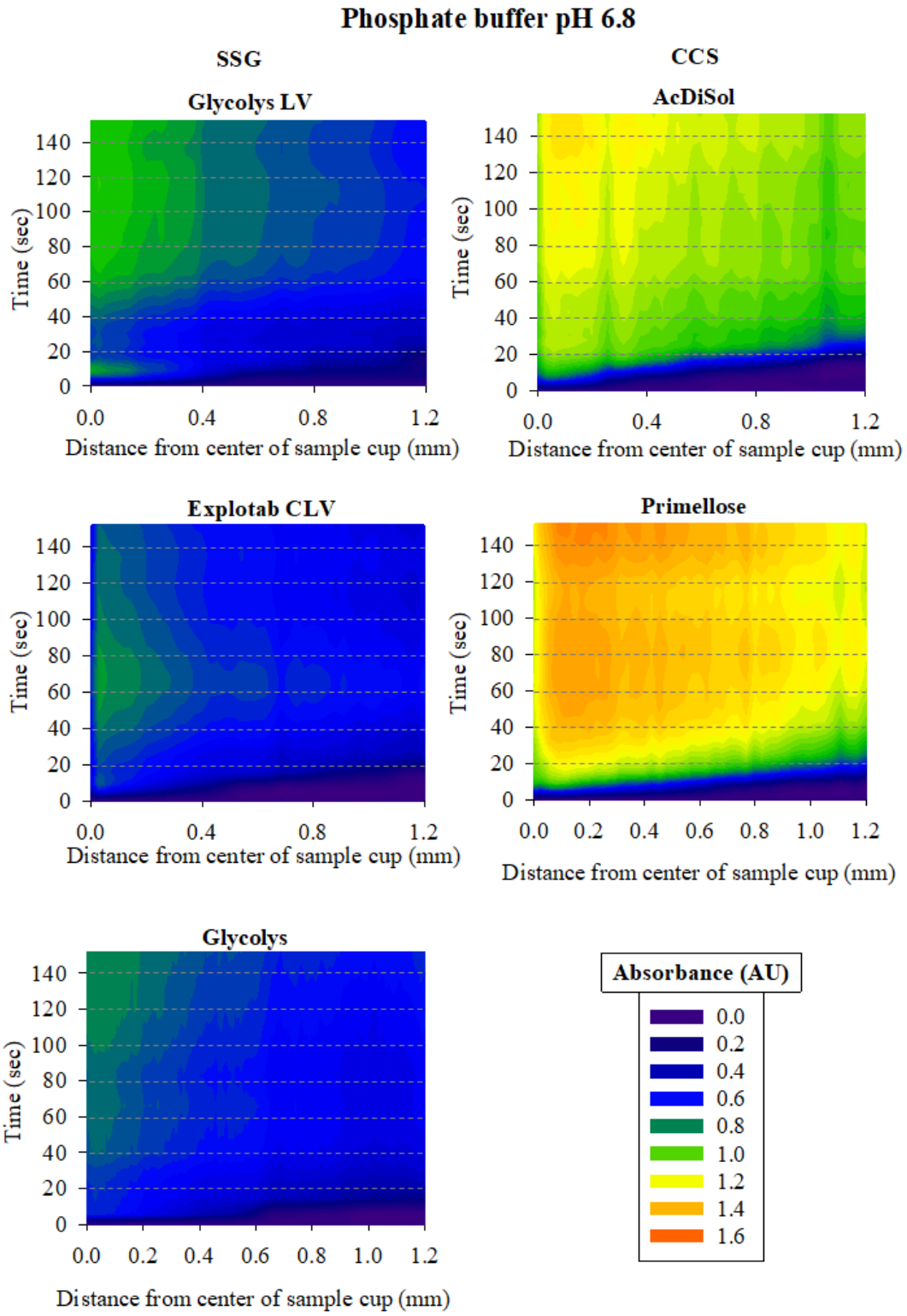

Figure 6.3: Absorbance values (Abs) of the studied superdisintegrant types and brands as a function of distance from the center of the sample cup (mm) in phosphate buffer pH 6.8 (SDi1, 0 mL/min, 37 °C, 254 nm) up to 2.5 min.

6.3.2. Impact of SSG variability on drug dissolution using real-time surface dissolution UV Imaging

6.3.2.1. Highly soluble drug (PRC)

The dissolution profiles and dissolution rates of PRC from drug compacts (control) and drug-SSG compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure 6.4**.

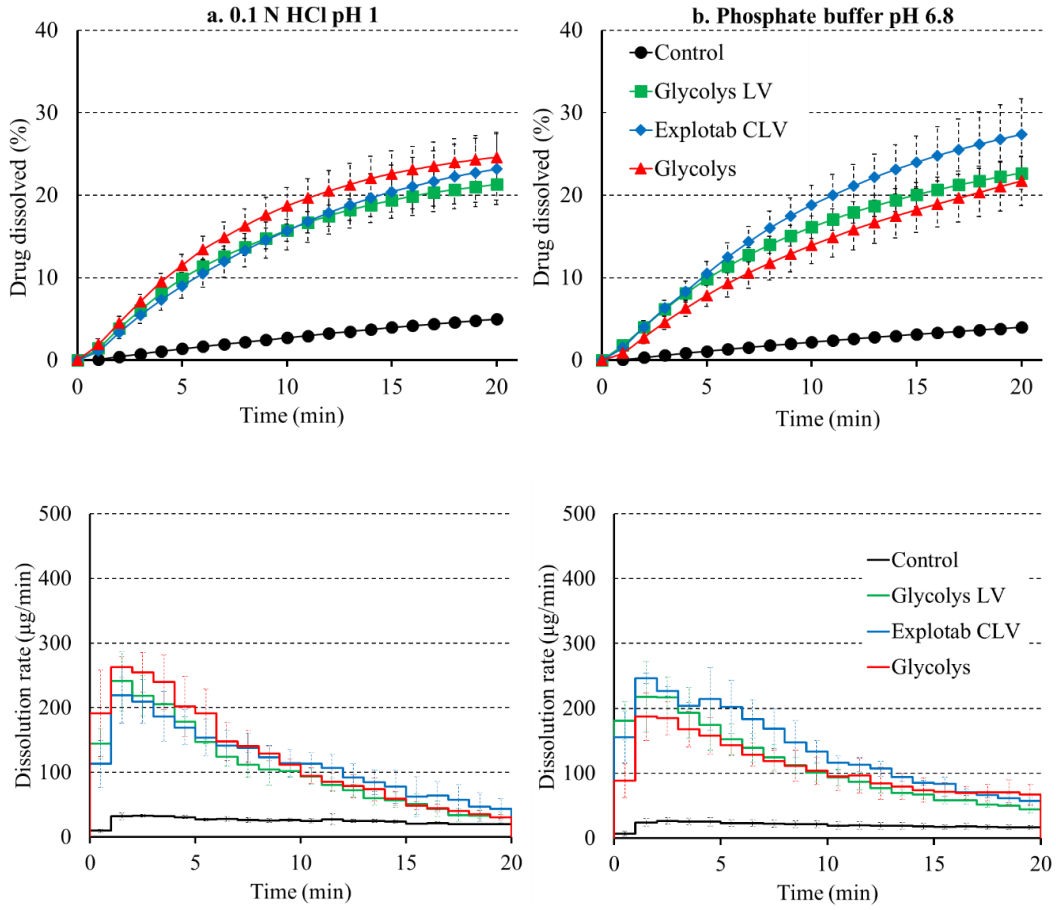

Figure 6.4: Cumulative % dissolved (top) and dissolution rates (bottom) of PRC from compacts in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the studied SSG brands (Glycolys LV: green squares/colour, Explotab CLV: blue diamonds/colour, Glycolys: red triangles/colour). (Mean ±SD, n =3)

Approximately 5% of PRC dissolved from the drug compact in 20 min in both media. The % of drug dissolved in 20 min from the drug-SSG compacts was increased in 0.1 N HCl pH 1 (21%, 23% and 25% of drug dissolved in the presence of Glycolys LV, Explotab CLV and Glycolys, respectively) and in phosphate buffer pH 6.8 (22%, 27% and 21% of drug dissolved in the presence of Glycolys LV, Explotab CLV and Glycolys, respectively). The dissolution rate of PRC from drug compacts was slow during the experiments in both media studied (dissolution rates of approximately 20 μg/min and 17 μg/min in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 at 20 min, respectively). Drug dissolution from drug-SSG compacts was faster compared to drug dissolution from drug compacts in the studied media, especially at early time points (1 – 5 min), as indicated by the increased dissolution rates of PRC in excipient presence (dissolution rates of approximately 200 μg/min from compacts containing Glycolys LV, Explotab CLV and Glycolys at 5 min in both media). This could be explained by the fast excipient hydration and swelling (excipient swelling at a distance of 1.2 mm from the centre of the sample cup within the first 40s, section 6.3.1) improving compact wetting [25]. Compact disintegration may also have contributed to the faster drug dissolution from drug-excipient compacts compared to drug compacts, as spread particles around the compact surface were observed after the end of each experiment only for the drug-excipient compacts. Comparison of the AUCs of the dissolution profiles revealed that drug dissolution was more complete in from the drug compacts compared to drug dissolution from the drug compacts (REs > 25%) (**Figure 6.5a**).

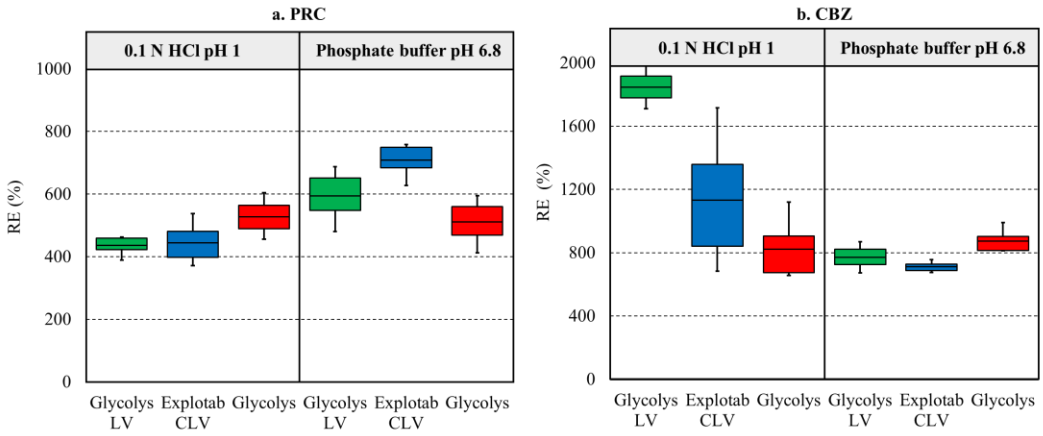

Figure 6.5: Relative effects of excipients on the AUCs of the dissolution profiles for a. PRC and b. CBZ in presence of the studied SSG brands (Glycolys LV: green colour, Explotab CLV: blue colour, Glycolys: red colour) in 0.1 N HCl pH 1 and phosphate buffer pH 6.8.

Differences in PRC dissolution from drug-SSG compacts in acidic and basic conditions for the studied SSG brands were not observed (REs of approximately 5%, 20% and -20% for Glycolys LV, Explotab CLV and Glycolys, respectively). The observed minor REs indicate that the pH-depended swelling performance of SSG (section 6.3.1) may not significantly affect the dissolution of a highly soluble drug between acidic and basic conditions.

6.3.2.2. Poorly soluble drug (CBZ)

The dissolution profiles and dissolution rates of CBZ from drug compacts (control) and drug-SSG compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure 6.6**.

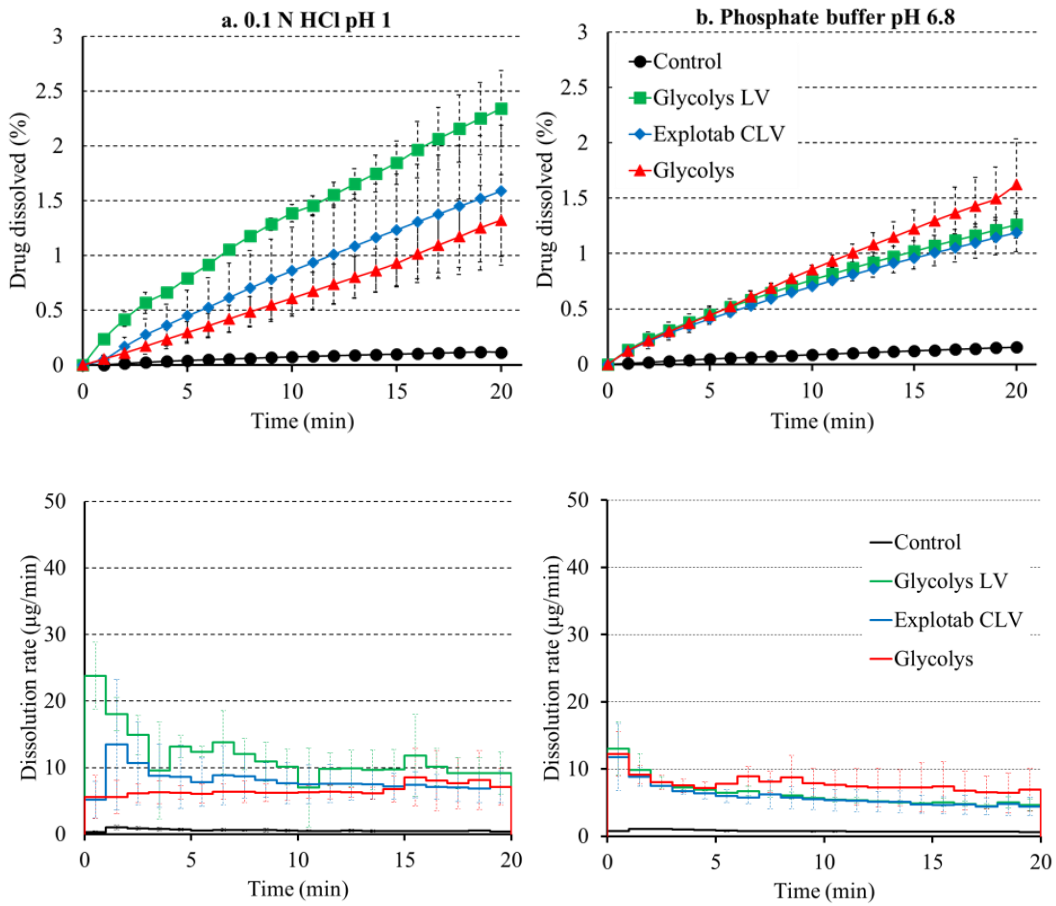

Figure 6.6: Cumulative % dissolved (top) and dissolution rates (bottom) of CBZ from compacts in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the studied SSG brands (Glycolys LV: green squares/colour, Explotab CLV: blue diamonds/colour, Glycolys: red triangles/colour). (Mean ±SD, n =3)

Approximately 0.1% of CBZ dissolved from the drug compact in 20 min in both 0.1 N HCl pH and phosphate buffer pH 6.8. In 0.1 N HCl pH 1, 2.3%, 1.6% and 1.3% of drug dissolved in 20 min in presence of Glycolys LV, Explotab CLV and Glycolys, respectively. The % of CBZ dissolved in excipient presence in phosphate buffer pH 6.8 in 20 min was similar between the different drug-excipient compacts (approximately 1.5% of CBZ dissolved from drug-excipient compact containing Glycolys LV, Explotab CLV, Glycolys). The rate of drug dissolution from the drug compact was slow in both sets of media (dissolution rates of approximately 0.5 µg/min

at 20 min in 0.1 N HCl pH 1 and phosphate buffer pH 6.8). CBZ dissolution was faster in SSG presence, especially at early time points (1 - 5 min), potentially due to the fast excipient swelling or compact disintegration (as explained in the case of PRC). In 0.1 N HCl pH 1, the dissolution rates of CBZ from drug-excipient compacts were 13 μg/min, 8.6 μg/min and 6.2 μg/min at 5 min in presence of Glycolys LV, Explotab CLV and Glycolys, respectively. The lower amount of drug dissolved in presence of Glycolys compared to the low viscosity brands (Glycolys LV, Explotab CLV) may be explained by the increase in the viscosity of the medium by high viscosity Glycolys [1]. The pronounced differences in the CBZ dissolution rates from compacts containing the low and high viscosity SSG brands are diminished at late points. Faster CBZ dissolution in presence compared to absence of excipient was also observed in phosphate buffer pH 6.8, with the dissolution rates from the three drug-excipient compacts being similar (CBZ dissolution rates of approximately 7 μg/min at 5 min in presence of the three studied SSG brands). CBZ dissolution in presence of excipient was more complete compared to the excipient absence (REs > 25%) (**Figure 6.5b**). Differences in drug dissolution from drug-excipient compacts between acidic and basic conditions were observed. For the low viscosity brands (Glycolys LV, Explotab CLV), the REs on the AUCs of the dissolution profiles between acidic and basic conditions were negative (REs of -45% and -20% for Glycolys LV and Explotab CLV, respectively), indicating that the improvement in CBZ dissolution is less pronounced in phosphate buffer pH 6.8 compared to 0.1 N HCl pH 1. As superdisintegrants swell more extensively in basic compared to acidic conditions due to their ionization [7], the presence of a highly swelled layer on top of the sample cup may add a physical or diffusive barrier for the release of poorly soluble drugs [18], despite the faster polymer water uptake in basic conditions (as explained previously in section 6.3.1). The swelling of the high viscosity Glycolys is as well more extensive in basic compared to acidic conditions, however comparison of CBZ dissolution profiles from compacts containing Glycolys between basic and acidic media reveal slightly more complete dissolution in phosphate buffer pH 6.8 (REs of 30%). This positive RE on the AUCs of the dissolution profiles may relate to the gelling effects of Glycolys [1] and the slower CBZ dissolution observed in 0.1 N HCl pH 1 (compared to the other two excipient brands).

6.3.3. Impact of CCS variability on drug dissolution using real-time surface dissolution UV Imaging

6.3.3.1. Highly soluble drug (PRC)

The dissolution profiles and dissolution rates of PRC from drug compacts (control) and drug-CCS compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure 6.7**.

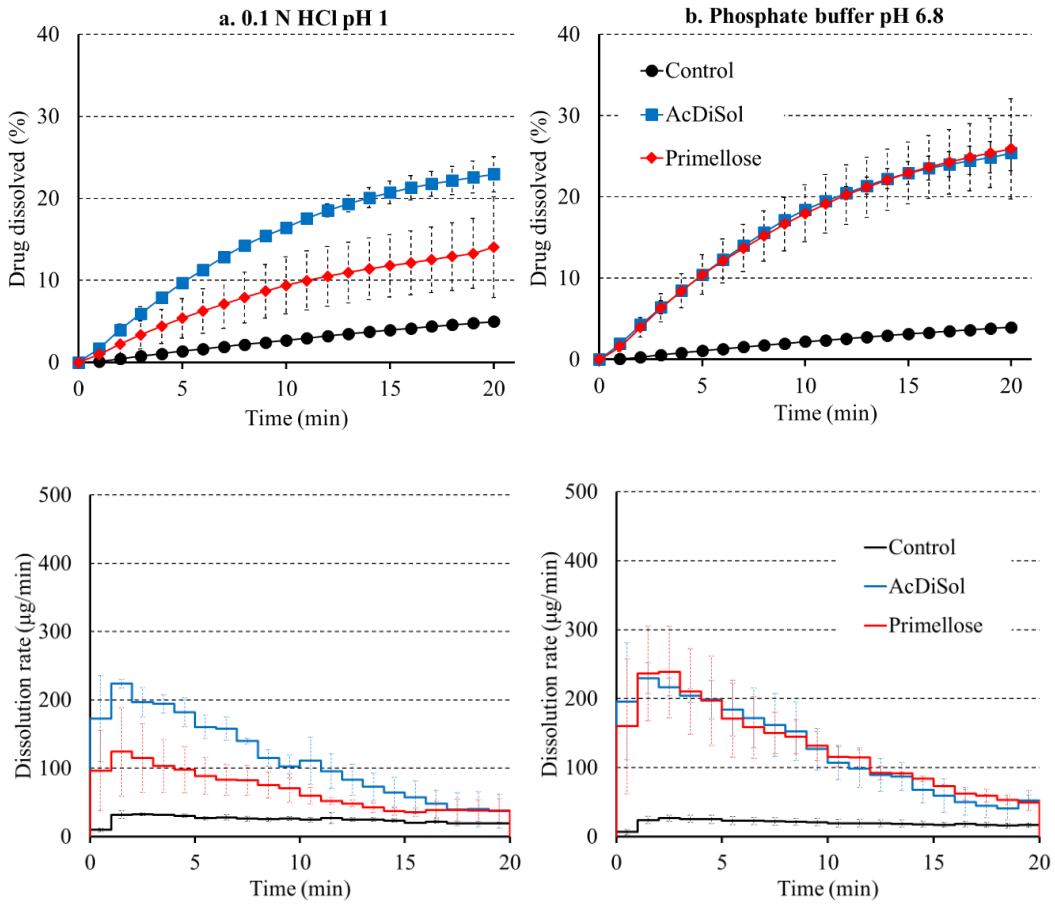

Figure 6.7: Cumulative % dissolved (top) and dissolution rates (bottom) of PRC from compacts in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the studied CCS brands (AcDiSol: blue squares/colour, Primellose: red diamonds/colour). (Mean ±SD, n =3)

A higher % of drug dissolved in 20 min was observed in excipient presence in 0.1 N HCl pH 1 (AcDiSol: 23%, Primellose: 14%) and phosphate buffer pH 6.8 (AcDiSol: 25%, Primellose: 26%) compared to the % of PRC dissolved from the drug compact

(5% of drug dissolved in 20 min). Faster drug dissolution was revealed in excipient presence compared to excipient absence in both media which may be explained by the enhancement in compact wetting or compact disintegration due to the hydrophilicity and swelling of CCS [1]. Differences in drug dissolution rates from the studied drug-CCS compacts were observed at early time points in 0.1 N HCl pH 1 as the dissolution rate of PRC was lower in presence of Primellose (98 μg/min of drug dissolved at 5 min) compared to AcDiSol (182 μg/min of drug dissolved at 5 min), probably due to the presence of larger excipient particles (Primellose) on top of the compact surface (section 6.3.1). In phosphate buffer pH 6.8 similar drug dissolution was observed between the drug-CCS compacts containing AcDiSol and Primellose (dissolution rates of approximately 200 μg/min in presence of both CCS brands at 5 min). At late time points, the dissolution rate of PRC gradually decreased in presence of the CCS brands in both media and any differences in drug dissolution between the studied CCS brands were diminished. Comparison of the AUCs of the dissolution profiles of the drug and drug-CCS compacts revealed significantly more complete dissolution from compacts containing excipient (REs > 25%) (**Figure 6.8a**).

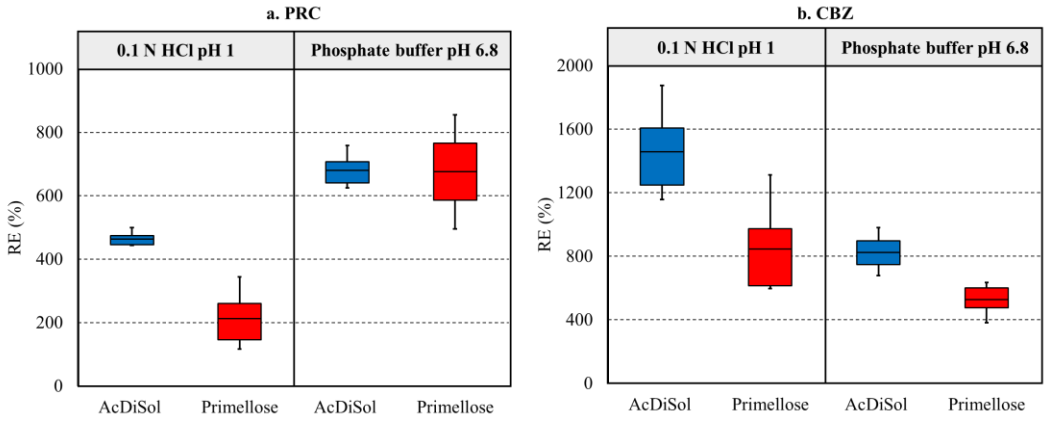

Figure 6.8: Relative effects of excipients on the AUCs of the dissolution profiles for a. PRC and b. CBZ in presence of the studied CCS brands (AcDiSol: blue colour, Primellose: red colour) in 0.1 N HCl pH 1 and phosphate buffer pH 6.8.

Differences in drug dissolution from drug-AcDiSol compacts between acidic and basic conditions were not observed, as revealed by the REs of AcDiSol on the AUCs of the dissolution profiles between acidic and basic conditions (RE = 10%). Drug

dissolution from the drug-Primellose compacts was significantly more complete in phosphate buffer pH 6.8 compared to 0.1 N HCl pH (RE = 97%), potentially due to the presence of larger excipient particles in 0.1 N HCl pH 1.

6.3.3.2. Poorly soluble drug (CBZ)

The dissolution profiles and dissolution rates of CBZ from drug compacts and drug-CCS compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure 6.9**.

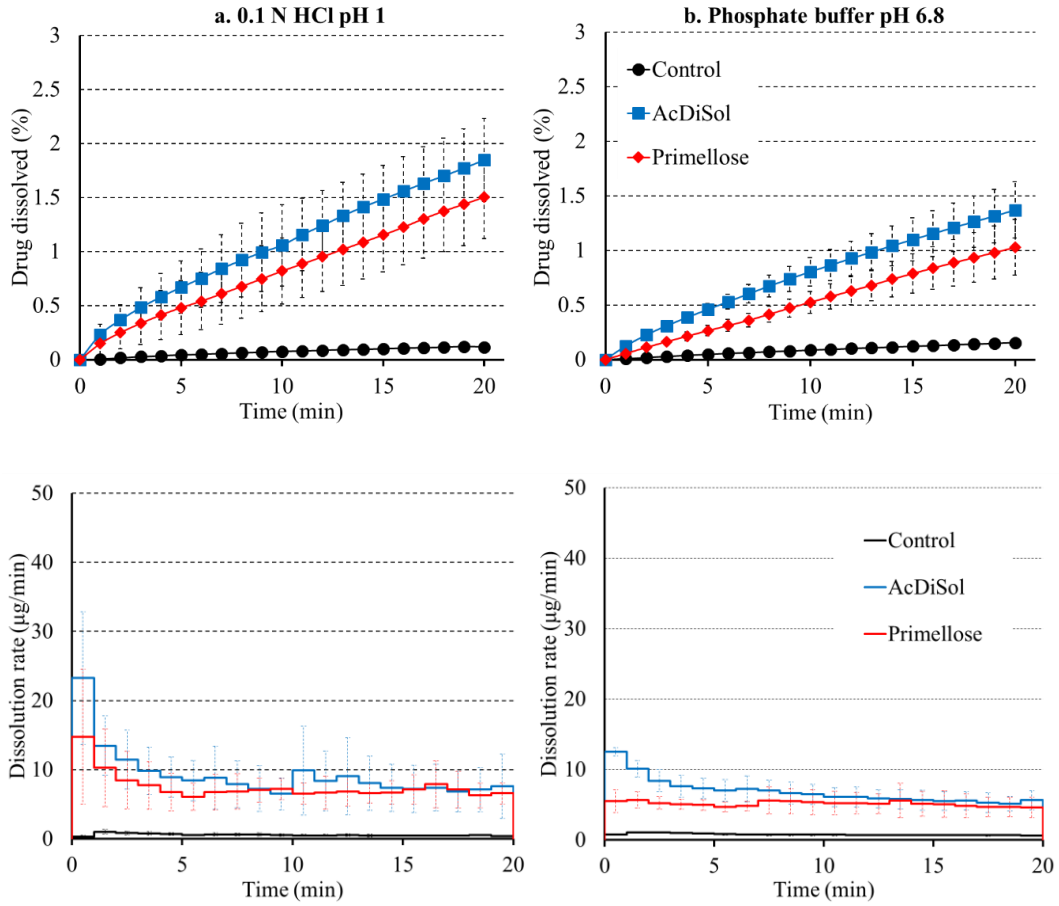

Figure 6.9: Cumulative % dissolved (top) and dissolution rates (bottom) of CBZ from compacts in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV imaging (1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the studied CCS brands (AcDiSol: blue squares/colour, Primellose: red diamonds/colour). (Mean ±SD, n =3)

CBZ dissolution reached approximately 1.8% and 1.5% from compacts containing AcDiSol and Primellose, respectively in 0.1 N HCl pH 1 and 1.3% and 1.0% in phosphate buffer pH 6.8. The fast excipient swelling at early time points (section 6.3.1) resulted in faster drug dissolution from drug-CCS compacts compared to the drug compacts in both sets of media, especially at early time points. Drug dissolution was slower in presence of Primellose (7 μg/min and 5 μg/min in acidic and basic conditions, respectively) compared to AcDiSol (9 μg/min and 7 μg/min in the acidic and basic medium, respectively), probably due to the presence of larger excipient particles (Primellose) on top of the compact surface (section 6.3.1). Differences in drug dissolution between the studied brands were smaller at late time points. In presence of excipient, drug dissolution was significantly more complete compared to the control sample in both experimental conditions (REs > 25%) (**Figure 6.8b**). The enhancement in CBZ dissolution by CCS presence was more pronounced in acidic compared to basic conditions (REs on the AUCs of the dissolution profiles between acidic and basic conditions of -30% and -20% for AcDiSol and Primellose, respectively). The faster water uptake of the excipients in basic media [7] would be expected to result in faster drug dissolution due to the improved compact wetting, however this is not observed as potentially the presence of a swelled layer on top of the compact surface created a physical or diffusive barrier delaying drug release [18].

6.3.4. Multivariate data analysis of *in vitro* dissolution data

The standardized coefficients of the variables for the SSG and CCS model are presented in **Figure 6.10**. The two models showed a good fit (SSG: $R^2 = 0.5$, CCS: $R^2 = 0.5$).

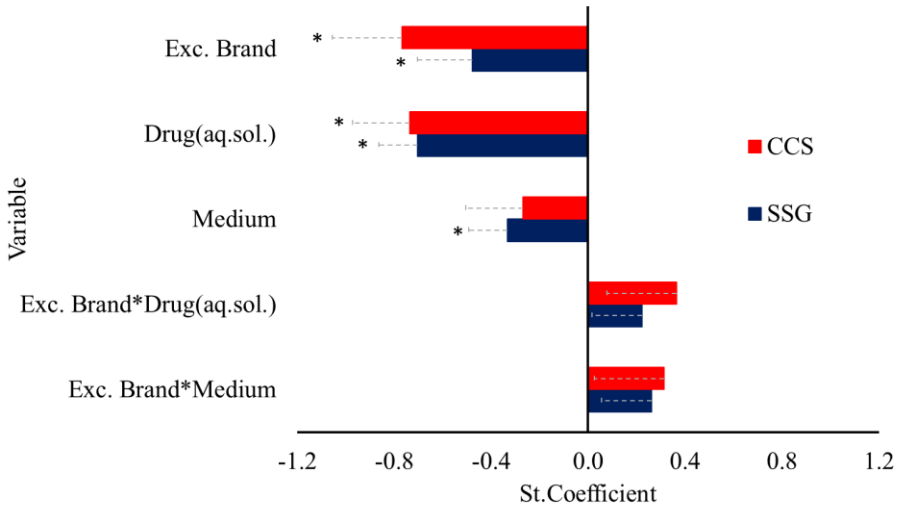

Figure 6.10: Standardized coefficients corresponding to the studied variables (and their interactions) for SSG (blue colour) and CCS (red colour). * denotes coefficients with $p < 0.05$. (Mean, - SE)

For SSG, excipient brand (negative effect, $p = 0.043$), $Drug_{aq.sol.}$ (negative effect, $p < 0.001$) and medium (negative effect, $p = 0.047$) were the critical variables in the model. The negative effect of the excipient brand indicates that increasing the viscosity type of SSG resulted in less pronounced dissolution enhancement compared to the low viscosity SSG brands. Enhanced compact wetting by low viscosity SSG brands is expected due to their faster water uptake and higher swelling [26]. Formation of gelling layer by high viscosity SSG brands which delays drug dissolution [1] could also explain this finding. The impact of varying SSG viscosity was more pronounced for the poorly soluble drug, indicated by the significance of the variable $Drug_{aq.sol.}$ in the model, as poorly soluble drugs will benefit more by an improvement in compact wetting. The negative effect of the variable medium reveals the pronounced enhancement in drug dissolution by SSG presence in acidic compared to basic conditions (especially, for the poorly soluble drug).

For CCS, excipient brand (negative effect, $p = 0.016$) and $Drug_{aq.sol.}$ (negative effect, $p = 0.006$) were critical variables in the model. Increasing the particle size of CCS will result in less pronounced improvement in drug dissolution probably due to the formation of physical or diffusive barrier for drug dissolution by larger excipient particles. The negative effect of the variable $Drug_{aq.sol.}$ indicates that the improved

wetting or compact disintegration by CCS presence will contribute more to the dissolution of poorly soluble drugs. The use of real – time surface dissolution imaging in combination with the multivariate data analysis revealed that CCS variability may be critical for the initial stages of drug dissolution, which could not be observed solely by the solubility experiments (chapter 4).

6.4. Conclusions

Superdisintegrant variability and interchangeability may be challenging for oral product performance, as the presence of superdisintegrants in pharmaceutical formulations directly affects drug dissolution. In this study, the use of real – time surface dissolution UV imaging confirmed the fast swelling ability of SSG and CCS. The swelling of the aforementioned superdisintegrants, however, depended on the critical material attributes and the pH of the dissolution medium. Excipient interchangeability could be challenging for oral product performance, as the swelling behaviour of SSG and CCS differed within media of different pH. Presence of superdisintegrants in compacts containing highly and poorly soluble compounds resulted in significantly faster drug dissolution for both drugs probably due to the enhanced compact wetting or compact disintegration by the hydrophilic excipients. Excipient properties affected the extent of drug dissolution, as pronounced dissolution enhancement was observed by low viscosity SSG or low particle size CCS brands, especially for the poorly soluble drug. In superdisintegrant presence, an interplay between drug aqueous solubility and medium characteristics was found that could affect product performance. For the highly soluble compound, the increased hydration capacity of superdisintegrants resulted in faster drug dissolution in basic compared to acidic conditions. The opposite was observed for the poorly soluble drug, as potentially the presence of swollen structure on top of the compact surface limited drug dissolution. SSG viscosity type, CCS particle size and drug aqueous solubility were considered critical biopharmaceutical factors affecting the performance and the impact of superdisintegrant variability on drug dissolution.

Acknowledgements

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Chapter 6 Commentary

Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) are superdisintegrants used in immediate release formulation to promote fast tablet disintegration. In this chapter, the swelling performance and impact on drug dissolution of three different viscosity SSG brands (Glycolys LV, Explotab CLV, Glycolys) and two different particle size distribution (PSD) CCS brands (AcDiSol, Primellose) were investigated using surface dissolution UV imaging. The fast and extensive excipient swelling was demonstrated, especially in basic conditions where the excipients are highly ionized. Differences in the swelling behaviour between SSG and CCS were revealed in both media, indicating that excipient interchangeability need to be thoroughly considered. Dissolution studies for a highly and a poorly soluble drug revealed faster and more complete dissolution in excipient presence for the studied drugs, attributed to the improved compact wetting or compact disintegration. The properties of SSG and CCS mostly affected the dissolution of the poorly soluble drug, as slightly faster drug dissolution was observed in presence of low viscosity SSG or low particle size CCS. The improvement in the dissolution of the highly soluble drug was more pronounced in the basic compared to the acidic medium in SSG or CCS presence as the fast excipient swelling improved powder solubilization. The opposite was found for the poorly soluble drug, as potentially the presence of a swelled layer on top of the powder surface delayed drug release. The need for the biopharmaceutical evaluation of the impact of excipients on drug dissolution was demonstrated as the enhancement in drug dissolution in excipient presence depended on the pH of the medium and drug aqueous solubility.

Conclusions and Future Perspectives

Conclusions

The QbD initiative requires the scientific understanding of the components and processes whose variability may affect final product qualities. Excipients constitute a large portion of pharmaceutical formulations and excipient variability or variation may affect oral drug bioavailability. Identification of the critical biopharmaceutical factors of excipients on oral drug performance would be beneficial for the development of robust formulations.

A literature review (chapter 1) identified the critical material attributes (molecular/structural/particle properties, level) of key excipient types commonly used in immediate release formulations. The need for investigating the biopharmaceutical implications of excipient variability was demonstrated. Based on this analysis, lubricants (MgSt), binders (HPMC) and superdisintegrants (SSG, CCS, CPV) were selected for further experimentation as their direct impact and their unclear mechanistic role on drug dissolution was highlighted.

Differences in drug apparent solubility in presence of varying excipient types and brands that could further complicate the rate and extent of drug absorption *in vivo*, were demonstrated (Chapters 2-4). MgSt and HPMC were flagged as excipients of high criticality for oral drug performance as significant changes in drug solubility at 24 hours were observed for the majority of compounds. Excipient effects on drug solubility strongly related to excipient critical material attributes, drug physicochemical properties (drug ionization, drug aqueous solubility) and medium characteristics (gastric, intestinal). The potential risks of excipient presence or variability on drug apparent solubility that could be critical for product performance were demonstrated with the use of multivariate data analysis and the design of roadmaps.

The impact of excipient variability was extended on drug dissolution and it was revealed that implications on product performance may be expected according to excipient type and drug characteristics (Chapter 5). Significantly faster dissolution was observed for a highly soluble compound when decreasing the particle size of MgSt with potential implications on quality control tests, regulatory approvals and drug

bioavailability. The experimental *in vitro* conditions need to be carefully selected, as the discriminatory power of the dissolution method depended on hydrodynamic characteristics. Varying HPMC or SSG viscosity type was not found critical for drug dissolution. A mechanistic understanding of the impact of excipient variability was provided with the use of real – time surface dissolution imaging.

Finally, the effects of critical excipient material attributes on the swelling performance and on drug dissolution for two commonly used superdisintegrants (SSG, CCS) were visualized with the use of real – time surface dissolution (Chapter 6). Excipient swelling depended on excipient (viscosity, PSD) and medium (pH) characteristics. The improvement in the dissolution of a highly and a poorly soluble drug by the excipients was imaged and attributed to the improved compact wetting or compact disintegration. An interplay between excipient, drug, medium characteristics and the extent of dissolution enhancement was revealed.

Summarizing, the critical properties and biopharmaceutical factors that may present risks for oral drug performance for three excipient types (lubricants, binders, superdisintegrants) have been identified. The results indicate that presence of excipients and excipient variability can influence drug dissolution *in vitro*. Changes in the amount of drug dissolved in the gastrointestinal lumen can be anticipated that could result in treatment failure or patient harm. The design of biorelevant methods to evaluate excipient criticality enables the appropriate selection of excipients and results in the production of robust formulations with the minimization of the potential *in vivo* risks. Moreover, the scientific understanding of the impact of excipients on drug product performance can improve the effectiveness of the pharmaceutical manufacturing processes reducing batch inconsistencies and failures, improving the cost effectiveness and resulting in a faster industrial response to market demands or shortages. Finally, the effective control of excipient variability on product performance through the creation of design spaces will minimize the regulatory constraints leading to fast product approvals without compromising patient safety.

Future Perspectives

In this project, the criticality of excipients and excipient variability for oral drug performance was demonstrated and a strong interplay between excipient critical material attributes, drug physicochemical characteristics, medium and hydrodynamic

characteristics was found. The results of this thesis could be considered as a good starting point for the construction of design spaces (according to the principles of the QbD initiative) demonstrating the limits within which changes in product performance by excipient variability or variation are not anticipated.

Towards this goal, further investigations are needed to delineate the changes in drug solubility in excipient presence. Use of material characterization techniques such as Raman spectroscopy, Differential Scanning Calorimetry, X-Ray Powder Diffraction etc, to identify potential structural changes in the physical mixtures or drug-excipient interactions could enhance the understanding of the observed effects of excipients on drug solubility in a molecular level. The use of surface dissolution UV imaging for other excipient types (binders, lubricants) would also be beneficial. Moreover, collection of additional data is necessary to properly outline and characterize the impact of excipient variability on product performance. This could be achieved by widening the range of the studied excipient properties (more than 2 levels) and broadening the data sets with other excipient types and/or drug with various physicochemical properties (e.g. drug ionization). Work should also focus in the investigation of other dosage forms (e.g. extended release formulations) as variability in more complex excipients (coating systems, release controlling agents, solubilizers) could be detrimental for oral drug absorption. Finally, as the varying composition of the gastrointestinal tract was found critical for the impact of excipients and excipient variability on drug dissolution, designing biorelevant tests simulating the fed state conditions (use of milk-based media, Fed State Simulated Gastric Fluid, Fed State Simulated Intestinal Fluid) could expand current knowledge and delineate the interplay between oral drug administration and meal intake.

Declaration of authorship

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Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.								
Signed					**Date**				